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A

FISH & RICHARDSON P.C.

225 Franklin Street
Boston, Massachusetts
02110-2804

Telephone
617 542-5070

Facsimile
617 542-8906

Web Site
www.fr.com

Frederick P. Fish
1855-1930

W.K. Richardson
1859-1951

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Box Patent Application

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Presented for filing is a new continuation-in-part patent application of:

Applicant: SHIN-ICHI FUNAHASHI AND SHOJI MIYATA

Title: PROTEIN HAVING PDZ DOMAIN SEQUENCE

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Enclosed are the following papers, including those required to receive a filing date under 37 CFR § 1.53(b):

	Pages
Specification	63
Claims	4
Abstract	1
Declaration	[To be Filed at a Later Date]
Drawing(s)	26

Enclosure:
— Postcard.

This application is a continuation-in-part (and claims the benefit of priority under 35 USC 120) of PCT/JP98/03603, filed August 12, 1998. The disclosure of the prior application is considered part of (and is incorporated by reference in) the disclosure of this application.

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JANIS K. FRASER, PH.D., J.D.
Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804

Respectfully submitted,

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Enclosures

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Attorney's Docket No.: 06501-056001

APPLICATION

FOR

UNITED STATES LETTERS PATENT

TITLE: PROTEIN HAVING PDZ DOMAIN SEQUENCE

APPLICANT: SHIN-ICHI FUNAHASHI AND SHOJI MIYATA

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PROTEIN HAVING PDZ DOMAIN SEQUENCE

This is a continuation-in-part of PCT/JP98/03603 filed August 12, 1998, and claims priority from Japanese Patent Application Nos. 9/230356, filed August 12, 1997, and 10/189944, filed June 18, 1998.

Technical Field

The present invention relates to novel proteins having the PDZ domain sequence and also to gene encoding the proteins.

Background Art

Proteins such as PSD-95, hDlg, ZO-1, p55, Dsh, LIN-7, InaD, and PTPL1/FAP1 are known to possess the PDZ domain and are called the PDZ family. A structure having approximately 80 to 90 amino acid residues, repeated three times and each containing a conserved "Gly-Leu-Gly-Phe (GLGF)" 4 amino acid motif (Neuron 9:929-942 (1992)), was initially identified in the 95 KDa post-synaptic density protein, PSD-95. The same domain structure was later found in the Drosophila lethal (1) discs large-1 tumor suppressor protein, DlgA (Cell 66:451-464 (1991)), and in the tight junction protein, ZO-1 (J. Cell Biol. 121:491-502 (1993)). The repeat sequence was therefore named the "PDZ domain" by combining the initials of PSD-95, DlgA, and ZO-1. (It is also called the "GLGF repeat" or "DHR (DlgA homology region) domain.") A protein having the PDZ domain is known to bind to other proteins by means of the sequence of this PDZ domain. For example, the PSD-95 protein is known to bind to the NMDA receptor 2B (Kornau, H. C., et al., Science 269:1737-1740 (1995)) and the Shaker-type K^+ channel (Kim, E., et al., Nature 378:85-88 (1995)). The hDlg

protein has been reported to bind directly to the protein encoded by the adenomatous polyposis coli tumor suppressor gene/APC (Matsumine et al., Science 272:1020-1023 (1996)), and the Dsh protein has been reported to bind directly to the Notch protein (Axelrod, J. D., et al., Science 271:1826-1832 (1996)). Furthermore, the InaD protein has been reported to bind to a Ca^{2+} channel protein, TRP, that functions in the Drosophila visual signal transduction cascade (Shieh, B. H. and Zhu, M. Y., Neuron 16:991-998 (1996)). The structure of proteins having the PDZ domain varies because some of the proteins contain only one domain (p55 and Dsh), while others contain two (SIP-1: Yanagisawa, J., et al., J. Biol. Chem. 272:7167-7172 (1997)), three (PSD-95 and hDlg), five (InaD and PTPL1/FAP1), seven (GRIP: Dong, H., et al., Nature 386:279-284 (1997)), or thirteen (Ullmer, C., et al., FEBS Letters 424:63-68 (1998)). Also a recently reported mouse gene lacks a region encoding an N-terminal peptide of the protein, but which encodes a peptide having four PDZ domains within this incomplete genetic region (Recorded to GenBank on May 18, 1997; accession number AF000168). Although there are a few exceptions, proteins having the PDZ domain are known to bind to other proteins that have a hydrophobic amino acid region consisting of three amino acids represented by "Thr/Ser-Xaa-Val" (Xaa being an arbitrary amino acid residue) at their C-terminus. Most of these proteins are transmembrane proteins and are presumed to function in signal transduction within the cell (TIBS 21:455-458 (1996), Yanagisawa, J., et al., J. Biol. Chem. 272:7167-7172 (1997)).

Since the above proteins having the PDZ domain and proteins that interact with these proteins are involved in

neural transmission, apoptosis, and malignant conversion, they have recently drawn attention as targets for developing pharmaceuticals.

Disclosure of the Invention

An objective of the present invention is to provide a novel protein having the PDZ domain sequence and a DNA encoding the protein. Another objective of the present invention is to provide a vector containing the DNA, a transformant harboring the DNA in which the DNA can be expressed, and a method of producing the recombinant protein utilizing the transformant. A further objective of the present invention is to provide an antisense DNA against the DNA and antibody that binds to the protein. Still another objective of the present invention is to provide a screening method for proteins that bind to the PDZ-domain protein.

While analyzing the changes of gene expression in human umbilical vascular endothelial cells by TNFα, the present inventors isolated a gene whose expression was increased by TNFα stimulation. Screening was performed using the gene as a probe, and, as a result, a gene encoding novel proteins was isolated. The present inventors analyzed the structure of the proteins encoded by the isolated gene and found that the proteins contain within the molecule the PDZ domain sequence that plays an important role in the interactions with other proteins involved in neural transmission, apoptosis, and malignant conversion. The present inventors also found that the single gene produces at least five different transcriptional products through the differences in transcription initiation sites and in splicing.

The present inventors succeeded in preparing the proteins encoded by the gene as recombinant proteins by incorporating the isolated gene into an expression vector, and by transfecting it into *E. coli* cells and culturing the cells. In addition, by immunizing rabbits with the proteins thus prepared, the present inventors succeeded in preparing antibodies that bind to the proteins.

The present invention relates to a group of novel proteins having the PDZ domain sequence within the molecule and to their gene, and more specifically, to

(1) a protein comprising the amino acid sequence described in SEQ ID NOs: 1, 2, 82, 83, or 84;

(2) a protein comprising the amino acid sequence described in SEQ ID NOs: 1, 2, 82, 83, or 84, in which one or more amino acids have been substituted, deleted, and/or added, and having affinities to other proteins characteristic to the PDZ domain;

(3) a fusion protein comprising the protein described in (1) or (2) and a protein or a peptide containing at least one antibody recognition site;

(4) a DNA encoding the protein of any one of (1) through (3);

(5) an antisense DNA against the DNA or a part thereof whose nucleotide sequence is described in SEQ ID NO: 2;

(6) a vector containing the DNA of (4);

(7) a transformant harboring the DNA of (4), in which the DNA can be expressed;

(8) a method of producing the protein of any one of (1) through (3), comprising the process of culturing the transformants described in (7);

(9) a screening method for proteins that bind to the protein of (1) or (2), comprising the process of selecting the proteins that bind to the proteins by contacting sample proteins with the proteins of any one of (1) through (3);

(10) a screening method for genes encoding the proteins that bind to the proteins of (1) or (2), comprising the process of selecting the genes corresponding to the gene products that bind to the proteins of (1) or (2) by contacting the gene products of the sample genes with the protein of (1) or (2);

(11) a protein that binds to the protein of (1) or (2);

(12) the protein of (11) that can be isolated by the method of (9);

(13) a gene encoding a protein that bind to the protein of (1) or (2);

(14) the gene of (13) that can be isolated by the method of (10); and

(15) an antibody that bind to the protein of (1) or (2).

In the present invention, the "PDZ domain sequence" refers to a sequence having 80 to 90 amino acids, containing the four amino acid motif that consists of "Gly-Leu-Gly-Phe" or similar amino acids (cf. TIBS 20:102-103 (1995)).

The present invention relates to novel proteins having the PDZ domain sequence. Although there are a few exceptions, proteins having the PDZ domain are known to interact with other proteins that have a hydrophobic amino acid region at their C-terminal ends. The other proteins are transmembrane proteins and are presumed to function in signal transduction within the cell (TIBS 21: 455-458

(1996), Yanagisawa, J., et al., J. Biol. Chem. 272:7167-7172 (1997)).

The present inventors have discovered five different transcription products among those that encode proteins having the PDZ domain. These products are thought to arise from a single gene through differences in transcription initiation sites and in splicing. The amino acid sequences of the proteins encoded by these transcription products are shown in SEQ ID NOs: 1, 2, 82, 83, and 84.

The protein having the amino acid sequence described in SEQ ID NO: 1, which is included in the proteins of the present invention, possesses nine PDZ domains that correspond to amino acid positions 69 to 158 (SEQ ID NO: 4), positions 371 to 461 (SEQ ID NO: 5), positions 520 to 615 (SEQ ID NO: 6), positions 649 to 734 (SEQ ID NO: 7), positions 782 to 865 (SEQ ID NO: 8), positions 928 to 1013 (SEQ ID NO: 9), positions 1024 to 1108 (SEQ ID NO: 10), positions 1161 to 1249 (SEQ ID NO: 11), and positions 1286 to 1373 (SEQ ID NO: 12)(see Figure 8).

Similarly, the protein having the amino acid sequence described in SEQ ID NO: 2, which is also included in the proteins of the present invention, corresponds to amino acids 369 to 1373 of the sequence described in SEQ ID NO: 1. The difference between the structures of these proteins is considered to arise from the difference in the mRNA transcription initiation sites.

The protein described in SEQ ID NO: 2 possesses a total of eight PDZ domain sequences, corresponding to amino acids 3 to 93, 152 to 247, 281 to 366, 414 to 497, 560 to 645, 656 to 740, 793 to 881, and 918 to 1005. However, it does not possess the first PDZ domain found in the protein described in SEQ ID NO: 1. Although its biological

significance is not clear, considering the specific expression of the mRNA corresponding to the protein described in SEQ ID NO: 2 in the liver (Example 5) and the fact that the PDZ domain plays an important role in protein-protein interactions, the protein described in SEQ ID NO: 2, by lacking this domain, may be involved in controlling the signal in the liver differently from the other tissues.

The protein having the amino acid sequence described in SEQ ID NO: 82 (the 32-8-1a protein), which is also included in the proteins of the present invention, consists of 2,000 amino acids. These amino acids are predicted by combining sequences of two cDNAs. One cDNA was discovered in the search for a cDNA derived from the human brain and contains a 5′ upstream region of a cDNA encoding a protein having the amino acid sequence described in SEQ ID NO: 1. The other cDNA (SEQ ID NO: 3) encodes the protein having the amino acid sequence described in SEQ ID NO: 1. The 32-8-1a protein possesses a total of 13 PDZ domain sequences, corresponding to amino acids 133 to 222, 253 to 335, 373 to 461, 549 to 632, 696 to 784, 1004 to 1087, 1147 to 1240, 1276 to 1361, 1409 to 1492, 1555 to 1640, 1651 to 1735, 1788 to 1870, and 1913 to 2000 (Figure 25).

Similarly, the amino acid sequences of the proteins encoded by the two splicing variants that are thought to result from the different splicing from the transcription product encoding the 32-8-1a protein and are also included in the proteins of the present invention, are shown in SEQ ID NO: 83 (the 32-8-1b protein) and in SEQ ID NO: 84 (the 32-8-1c protein). The 32-8-1b protein, similar to the 32-8-1a protein, consists of 2,070 amino acids, possessing 13 PDZ domains. The PDZ domains of the 32-8-1b protein exist

at positions 133 to 222, 253 to 335, 373 to 461, 549 to 632, 696 to 784, 1004 to 1087, 1147 to 1241, 1346 to 1431, 1479 to 1562, 1625 to 1710, 1721 to 1805, 1858 to 1946, and 1983 to 2070 of its amino acid sequence.

In contrast, the 32-8-1c protein has a shorter chain length than 32-8-1a or 32-8-1b because of the termination codon created by the splicing, and consists of 1,239 amino acids, possessing seven PDZ domains. The PDZ domains of the 32-8-1c protein exist at positions 133 to 222, 253 to 335, 373 to 461, 549 to 632, 696 to 784, 1004 to 1087, and 1147 to 1239 of its amino acid sequence.

It is clinically very significant that these proteins of the present invention are all of human origin, as opposed to being derived from other animals. In particular, proteins derived from other organisms (e.g., mice or rats) cause serious side effects such as reduction or loss of therapeutic effects by generating antibodies or by inducing serum sickness and anaphylactic shock, due to the immunogenicity when they are used to treat humans. Therefore, it is desirable to use proteins of human origin as therapeutic materials for humans.

The proteins of the present invention can be prepared from natural proteins, but they can also be prepared as recombinant proteins using recombinant genetics technology. The natural proteins can be isolated from such sources as the human umbilical vascular endothelial cells (HUVEC) by means of methods well-known to persons skilled in the art. For example, they can be isolated as described below, with an affinity column in which an antibody against the protein of the present invention has been bound to an appropriate support. The affinity column can be constructed, for example, according to the method described by Wilchek et

al. (Wilchek et al., Methods Enzymol. 104:3-55 (1984)). Furthermore, the recombinant protein can be prepared by culturing the cells transformed with the DNA encoding the protein of the present invention, as will be described later.

The proteins of the present invention also include functional derivatives of the proteins having the amino acid sequences described in SEQ ID NOs: 1, 2, 82, 83, and 84. A "functional derivative" means a protein that differs from the amino acid sequences described in SEQ ID NOs: 1, 2, 82, 83, and 84 by one or more amino acid residues through substitution, deletion, or addition, but that still maintains the affinity to the other proteins characteristic of the PDZ domain. This affinity normally arises from the affinity to a hydrophobic amino acid region that exists in the C-terminal ends of the other proteins. The hydrophobic amino acid region contains a hydrophobic amino acid motif represented by "Thr/Ser-Xaa-Val" (Xaa being an arbitrary amino acid residue) (cf. Science 269:1737 (1995), Nature 378:85 (1995), Science 277:1511 (1997), Neuron 20:693 (1998), Oncogene 16:643 (1998), J. Biol. Chem. 273:1591 (1998), Science 272:1020 (1996), Proc. Natl. Acad. Sci. USA 94:6670 (1997), Proc. Natl. Acad. Sci. USA 94:11612 (1997), J. Neurosci. 18:128 (1998), J. Neurosci. 16:7407 (1996), Nature Biotech. 15:336 (1997), FEBS Letters 409:53 (1997), Nature 386:284 (1997), Nature 386:279 (1997), Nature Structure Biol. 5:19 (1998), J. Neurosci. 16:24 (1996), J. Biol. Chem. 272:24191 (1997), Science 271:1826 (1996), TIBS 21:455 (1996), Cell 85:195 (1996), Neuron 18:95 (1997), Proc. Natl. Acad. Sci. USA 94:12682 (1997), J. Biol. Chem. 272:8539 (1997), J. Biol. Chem. 272:24333 (1997), J. Biol. Chem. 272:7167 (1997), Proc. Natl. Acad. Sci. USA 94:13683

(1997), Nature 392:6676 (1998), J. Biol. Chem. 272:32019 (1997), Mol. Biol. Cell 9:671 (1998)).

Functional derivatives occur naturally or can be produced artificially; both of these are included in the present invention. Methods to alter amino acids, which are well known to persons skilled in the art, include the methods developed by Kunkel et al. (Methods Enzymol. 85:2763-2766 (1988)) and those that utilize polymerase chain reaction (PCR). In the Kunkel method, uracil is incorporated by using dut^- or ung^- *E. coli* as a host when preparing the single-stranded DNA to be used as the template. Primers containing the desired mutations are annealed to this template containing uracil, and ordinary DNA synthesis is performed *in vitro*. When the double-stranded DNA thus produced with the uracil-containing DNA is introduced into ordinary *E. coli* cells, the uracil-containing DNA strand becomes degraded, and DNA synthesis proceeds with the mutated DNA strand as the template. As a result, DNA into which mutations have been introduced can be obtained with a very high efficiency. An example of the methods of introducing mutations using PCR follows. Two sets of primers are prepared. One of the primers in each set encompasses the region into which the mutation will be introduced, and the other contains a restriction enzyme recognition site or a sequence just outside of it. A region containing appropriate restriction enzyme sites is thus targeted. PCR reactions are then performed with the two sets of primers. After the products of the two PCR reactions are mixed, the DNA is amplified using primers having sequences corresponding to the recognition sites of the two restriction enzymes or the sequences just outside of them. The product is next digested with appropriate

restriction enzymes so that the resultant fragment contains the region into which the mutation has been introduced. The fragment thus obtained is substituted for the said region in the original DNA (Saiki et al., Science 239:487-491 (1988), Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley - Interscience Publishing, Unit 8.5.1-8.5.10 (1997), Supplement to Jikken Igaku (Experimental Medicine) "Shin Idenshi Kogaku Handbook (New Genetic Engineering Handbook)," Yohdosha, pp251-261). The desired number of amino acids to be substituted in a functional derivative is generally 10 or less, more preferably 6 or less, and still more preferably 3 or less.

The term "substantially pure" as used herein in reference to a given polypeptide means that the polypeptide is substantially free from other biological macromolecules. The substantially pure polypeptide is at least 75% (e.g., at least 80, 85, 95, or 99%) pure by dry weight. Purity can be measured by any appropriate standard method, for example, by column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

A "conservative amino acid substitution" is one in which an amino acid residue is replaced with another residue having a chemically similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine)

and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine).

The present invention also relates to the DNA encoding the proteins of the present invention described above. The DNA encoding the proteins of the present invention can be cDNA, genomic DNA, or synthetic DNA. The DNA of the present invention can be used, for example, to produce the proteins of the present invention as recombinant proteins. More specifically, the proteins of the present invention can be prepared as recombinant proteins by inserting the DNA encoding the proteins of the present invention into appropriate expression vectors, culturing the transformants obtained by introducing the said vectors into appropriate cells, and purifying the expressed proteins.

By hybridization under "stringent conditions" is meant hybridization at 37°C, 1 X SSC, followed by washing at 42°C, 0.5 X SSC.

The "percent identity" of two amino acid sequences or of two nucleic acids is determined using the algorithm of Karlin and Altschul (Proc. Natl. Acad. Sci. USA 87:2264-2268, 1990), modified as in Karlin and Altschul (Proc. Natl. Acad. Sci. USA 90:5873-5877, 1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al. (J. Mol. Biol. 215:403-410, 1990). BLAST nucleotide searches are performed with the NBLAST program, score = 100, wordlength = 12. BLAST protein searches are performed with the XBLAST program, score = 50, wordlength = 3. Where gaps exist between two sequences, Gapped BLAST is utilized as described in Altschul et al. (Nucleic Acids Res. 25:3389-3402, 1997). When utilizing BLAST and Gapped BLAST programs, the default

parameters of the respective programs (e.g., XBLAST and NBLAST) are used. See http://www.ncbi.nlm.nih.gov.

An "isolated nucleic acid" is a nucleic acid the structure of which is not identical to that of any naturally occurring nucleic acid or to that of any fragment of a naturally occurring genomic nucleic acid spanning more than three separate genes. The term therefore covers, for example, (a) a DNA which has the sequence of part of a naturally occurring genomic DNA molecule but is not flanked by both of the coding sequences that flank that part of the molecule in the genome of the organism in which it naturally occurs; (b) a nucleic acid incorporated into a vector or into the genomic DNA of a prokaryote or eukaryote in a manner such that the resulting molecule is not identical to any naturally occurring vector or genomic DNA; (c) a separate molecule such as a cDNA, a genomic fragment, a fragment produced by polymerase chain reaction (PCR), or a restriction fragment; and (d) a recombinant nucleotide sequence that is part of a hybrid gene, i.e., a gene encoding a fusion protein. Specifically excluded from this definition are nucleic acids present in mixtures of different (i) DNA molecules, (ii) transfected cells, or (iii) cell clones: e.g., as these occur in a DNA library such as a cDNA or genomic DNA library.

The cells to be used for producing the recombinant proteins include, but are not limited to, animal cells such as Chinese hamster ovary (CHO) cells, COS cells (a cell line obtained by transforming monkey CV-1 fibroblasts by the SV40 virus lacking the replication origin), mouse NIH3T3 cells, human HeLa cells, and human lymphoid Namalva cells (Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley - Interscience Publishing,

Unit 16.12-16.14 (1991)). As the vectors, pSV2neo, pcDNAI, pCD8, pRcRSV, pREP4, pCEP4 (Invitrogen), pMAM, pMAMneo (Clontech), pCI-neo mammalian expression vector, pSI-neo mammalian expression vector, pTARGET™ mammalian expression vector (Promega), and the like can be used. Both plasmid vectors and recombinant viruses can be constructed for producing the recombinant protein. Recombinant adenoviruses using the pAdex vector (Supplement to Jikken Igaku (Experimental Medicine) "Shin Idenshi Kogaku Handbook (New Genetic Engineering Handbook)," Yohdosha, pp238-244), the LN and LXSN vector series, the pBabe vector series (a modified version of the preceding series), recombinant retroviruses using such vectors as the MFG vectors (Supplement to Jikken Igaku (Experimental Medicine) "Shin Idenshi Kogaku Handbook (New Genetic Engineering Handbook)," Yohdosha, pp245-250, Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley - Interscience Publishing, Unit 9.10.1-9.14.3 (1992)), Sindbis viruses, and vaccinia viruses (Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley - Interscience Publishing, Unit 16.15.1-16.19.9 (1992)) can also be used to produce the recombinant proteins. It is also possible to produce the recombinant proteins by utilizing baculoviruses, and silkworm larvae. Alternatively, cultured cell lines such as SF21, SF9, and High Five™ cells can be used as the host (Supplement to Jikken Igaku (Experimental Medicine) "Bio Manual Series 7: Bunshi Seibutsu Kenkyu No Tame No Tanpakushitsu Jikken Hou (Protein Experimentation Methods for Molecular Biology Research)," Yohdosha, pp167-171 (1994), OReilly, D. R. et al., "Baculovirus Expression Vectors, A Laboratory Manual," Oxford University Press (1992)). As the baculovirus

expression vectors, pBacPAK8, 9, pBacPAK-His 1/2/3, pAcUW31 (Clontech), pBlueBac (Invitrogen), pBAC, pBACgus (Novagen), etc., can be used.

The promoters utilized to express the proteins efficiently in animal cells include, for example, the SV40 early promoter (Rigby In Williamson (ed.), Genetic Engineering, Vol. 3, Academic Press, London, pp83-141 (1982)), the EF-1α promoter (Kim et al., Gene 91:217-223 (1990)), the CAG promoter (Niwa et al., Gene 108:193-200 (1991)), the RSV LTR promoter (Cullen, Methods in Enzymology 152:684-704 (1987)), the SRα promoter (Takabe et al., Mol. Cell. Biol. 8:466 (1988)), the CMV early promoter (Seed and Aruffo, Proc. Natl. Acad. Sci. USA 84:3365-3369 (1987)), the SV40 late promoter (Gheysen and Fiers, J. Mol. Appl. Genet. 1:385-394 (1982)), the Adenovirus late promoter (Kaufman et al., Mol. Cell. Biol. 9:946 (1989)), the HSV TK promoter, and inducible expression promoters. The MMTV promoter induced by glucocorticoids, the MT (metallothionein) II promoter induced by phorbol esters or heavy metals, the Tet-On/Off system that can be turned on and off by tetracycline (Clontech), the expression system that can be induced by ecdysone (Invitrogen), and the Lac Switch expression system induced by IPTG are preferred examples of the inducible expression promoters.

It is also possible to use yeast cells to produce the proteins. Protease-deficient cell lines such as BJ2168, BJ926, and CB023, and cell lines for secretion vectors, such as 20B-12, can be used as hosts (Supplement to Jikken Igaku (Experimental Medicine) "Bio Manual Series 4: Idenshi Donyu To Hatsugen Kaisekihou (Gene Introduction and Expression Analysis Methods)," Yohdosha, pp166-176 (1994)). The expression vectors include pYEUra3 (Clontech), pYEX™-

BX, and pYEX™-S1. It is also possible to express the protein in fission yeast SP-Q01, using fission yeast expression vector pESP-1 (Stratagene). The PGK promoter and the ADH1 promoter, which are constitutive; the CUP1 promoter, which is inducible by copper ions; the Gal1-Gal10 promoter, which is induced by galactose and repressed by glucose; and the PHO5 promoter, which is induced by a reduction in phosphate concentrations and repressed by high phosphate concentrations are preferable as promoters that efficiently express the protein in the yeast cells. In fission yeast, promoters such as the nmt1 promoter are preferable.

Four broad categories of expression promoters can be used to produce recombinant proteins using *E. coli* cells. The λPL promoter is regulated by the clts857 repressor and is induced by heat shock. N4830-1 and M5219 can be used as the host, and vectors such as pPL-lambda, pKC30, and pRIT2T can be used for expression. The tac promoter is regulated by the $lacI^q$ repressor and is induced by adding isopropyl β-D-thiogalactoside (IPTG). JM105 and XL1-Blue can be used as the host, and vectors such as pDR540, pKK233-3, pGEX-3X, and pMAL-c2 can be used for expression. The trp promoter is regulated by the trp repressor and is induced by adding β indole acrylic acid (IAA). HB101 and the like can be used as the host; vectors such as pBTrp2 can be used for expression. The T7 phage promoter is recognized for expression by only the T7RNA polymerase. Therefore, the BL21(DE3) strain can be used as the host. This strain can be prepared by lysogenizing the *E. coli* BL21 strain with λ phage DE3, into which the lacI gene and a DNA fragment containing the T7RNA polymerase gene under the control of the lacUV5 promoter are inserted within its int gene. The

inducible expression directed by the T7 promoter becomes possible by adding IPTG, which induces the T7RNA polymerase. The vectors include pET-3c and pET-8c. BL21(DE3)pLysS contains, in addition to the above plasmid, a plasmid producing the T7 lysozyme. This lysozyme is a natural inhibitor that binds to the T7RNA polymerase and inhibits its transcription, in order to suppress the basal level T7RNA polymerase activity. Therefore, BL21(DE3)pLysS can also be used as the host. pET-11c, pET-11d, and the like, which possess the T7lac promoter with the lac operator sequence inserted downstream of the T7 promoter transcription initiation site, can also be used as the expression vector (Studier, F., et al., J. Mol. Biol. 189:113-130 (1996), Studier, F., et al., Methods Enzymol. 185:60-8 (1990)).

Methods of introducing the vector into the host include the electroporation method (Chu, G., et al., Nucl. Acids Res. 15:1311-1326 (1987)), the calcium phosphate method (Chen, C. and Okayama, H., Mol. Cell. Biol. 7:2745-2752 (1987)), the DEAE dextran method (Lopata, M. A., et al., Nucl. Acids Res. 12:5707-5717 (1984); Sussman, D. J. and Milman, G., Mol. Cell. Biol. 4:1642-1643 (1985)), and the lipofectin method (Derijard, B., Cell 7:1025-1037 (1994); Lamb, B. T., et al., Nature Genetics 5:22-30 (1993); Rabindran, S. K., et al., Science 259:230-234 (1993)), but any method can be used.

The recombinant protein can be purified from the transformant thus obtained by means of the gel filtration method, ion exchange chromatography, affinity chromatography, reverse phase chromatography, hydroxyapatite chromatography, hydrogen bonding chromatography, and chelating columns (Deutscher, M. P.,

ed., Methods Enzymol. 182, Guide to Protein Purification, 1990; Principles and Methods Series: Gel Filtration, Ion Exchange chromatography, and Affinity chromatography. Pharmacia). Antibodies against the protein of the present invention are prepared as described below, and the protein can be highly purified by means of affinity chromatography using the antibodies.

Persons skilled in the art can, by using the prepared protein of the present invention, easily prepare the antibodies that bind to it. The antibodies of the present invention can be obtained by expressing the gene of the present invention using an appropriate *E. coli* expression vector; purifying the product; and immunizing rabbits, mice, rats, goats, or chickens with it. It is also possible to synthesize peptides that correspond to appropriate regions of the protein encoded by the gene of the present invention, and to immunize the animals described above, thereby obtaining the antibodies to the gene product. Methods to establish mouse or rat hybridomas can be used to produce monoclonal antibodies (Kohler and Milstein, Nature 256:495-497 (1975)). Specifically, mice, rats, or Armenian hamsters are first immunized with the prepared protein of the present invention. The antibody-producing cells are then collected from the spleen or the lymph nodes and fused in vitro with myeloma cells, and clones are selected through screening using the antigen (Harlow, E. and Lane, D., Antibodies: A Laboratory Manual. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York (1988)). The mouse myeloma cells include p3-x63-Ag8-U1 (P3-U1), P3-NSI/1-Ag4-1 (NS-1), and SP2/0-Ag14 (AP2/0), and the rat myeloma cells include YB2/3HL.P2G11.16Ag20 (YB2/0). The cells can be fused using polyethylene glycol or

electric pulses. Monoclonal antibodies, such as that contained in the cultured supernatant of the hybridomas and that contained in the ascites of the mouse treated with an immunosuppressant and with the mass-cultured hybridoma injected into its abdominal cavity, can be purified by, for example, protein A-Sepharose (Pharmacia). Furthermore, monoclonal antibodies can also be purified using an affinity column having the protein of the present invention immobilized onto the support (Harlow, E. and Lane, D., Antibodies: A Laboratory Manual. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York (1988)).

When the antibodies thus obtained are administered to humans, it is beneficial to use a human or humanized antibody in order to reduce the immunogenicity. The methods to humanize antibodies include the CDR graft method, in which the antibody gene is cloned from the monoclonal antibody producing cells and the antigen determining region is transplanted to a known human antibody (Immunology Methods Manual 1: pp98-107, Academic Press). Human antibodies can also be produced by immunizing a mouse that has its immune system replaced with the human immune system, following a procedure similar to the one used with regular monoclonal antibodies. The human B cell hybridoma method (Kozbor, et al., Immunology Today 4:72 (1983)), and the Epstein-Barr virus (EBV) - Hybridoma method (Cole, et al. in Monoclonal Antibodies and Cancer Therapy, Ala R. Liss, Inc. pp77-96 (1985)) can also be used to produce monoclonal antibodies.

The antibodies thus obtained can be used not only to detect the proteins of the present invention and as antibody therapies, but also to screen the proteins

described below that interact with the proteins of the present invention.

The present invention also relates to the methods used to screen for the proteins that bind to the proteins of the present invention. The group of proteins having the PDZ domain, such as those of the present invention, share a common property of interacting with other proteins having the region of hydrophobic amino acids on the C-terminus. These and other binding proteins can be isolated by the screening methods of the present invention. These screening methods include the process to select the proteins that bind to the proteins of the present invention. In such a process, the sample proteins are brought into contact with the proteins of the present invention in the form of lysates from the cells or tissues that are expected to contain the target proteins.

An example of the specific methods is the immunoprecipitation method. The immunoprecipitation method is the most common method used to detect protein-protein binding. In immunoprecipitation, biological samples, such as lysates from cells or tissues, for example, cell lysates prepared by dissolving cells such as human umbilical vascular endothelial cells with Triton X-100 or sodium deoxycholate, are usually brought into contact with the proteins of the present invention. The antibodies are then applied to the complex thus formed between the proteins of the present invention with their binding proteins. The immune complexes thus formed are then precipitated (Supplement to Jikken Igaku (Experimental Medicine) "Shin Idenshi Kogaku Handbook (New Genetic Engineering Handbook)," Yohdosha, pp304-308 (1996)).

The immune complex can be precipitated by, for example, using protein A-Sepharose or protein G-Sepharose when the antibody is a mouse IgG antibody. General methods can be found, for example, in "Antibodies" (Harlow, E. and Lane, D., Antibodies. pp511-552, Cold Spring Harbor Laboratory Publications, New York (1988)). Moreover, methods based on those described above can generally be used even in the case of antibodies from other animal species.

The proteins of the present invention, which are used in the immunoprecipitation, can have a recognition site (epitope) for the monoclonal antibody, whose specificity has been well characterized, that is introduced into the N-terminus or the C-terminus of the proteins. The proteins have thus been made into fusion proteins with the epitope, and the immune complexes can be formed by reacting the antibody to the epitope.

A variety of epitope-antibody systems are commercially available, and these can also be used (Jikken Igaku (Experimental Medicine) 13:85-90 (1995)). Some commercially available vectors can express relatively large fusion proteins, such as those with β-galactosidase, maltose-binding protein, glutathione S-transferase, and Green fluorescent protein, by incorporating the DNA encoding the desired protein through multi-cloning sites. In order to minimize the changes in the properties of the desired protein due to fusing, methods have been reported in which only a small epitope portion having several to a dozen or so amino acids is inserted. For example, the epitopes in poly-histidine (His-tag), influenza hemagglutinin HA, human c-myc, FLAG, vesicular stomatitis virus glycoprotein (VSV-GP), T7 gene 10 protein (T7-tag),

human herpes simplex virus glycoprotein (HSV-tag), E-tag (an epitope on a monoclonal phage), etc., and their corresponding antibodies that recognize the epitopes can be used (Jikken Igaku 13: 85-90 (1995)). Any other epitope-antibody system can be used, as long as it can detect the fusion protein. It should be noted that the fusion proteins that bind to the proteins of the present invention can be isolated by means of affinity chromatography, without using antibodies. For example, the glutathione-Sepharose 4B column can be used for a GST-fusion protein.

SDS-PAGE is generally used to analyze the immunoprecipitated proteins. In this method, gel of an appropriate concentration is used according to the molecular weights of the proteins so that the bound proteins can be analyzed. It is generally difficult to detect the bound proteins with ordinary staining methods for proteins (e.g., the Coomassie Brilliant Blue (CBB) staining method or the silver staining method). However, the cells can be cultured in a medium to which ^{35}S-methionine or ^{35}S-cysteine has been added to label the proteins, in order to increase the detection sensitivity. Once the molecular weight of a protein becomes known, it is possible to purify the protein directly from the SDS-polyacrylamide gel and to determine its sequence. In addition to the immunoprecipitation method described above, it is also possible to prepare the proteins by running the culture supernatant or the cellular extracts of the cells expected to express the proteins that bind to the proteins of the present invention through an affinity column having the proteins of the present invention immobilized onto it, then purifying the proteins that specifically bound to the column.

It is also possible to directly screen for the genes encoding the proteins that bind by using the proteins of the present invention. In this screening method, the gene products of the sample genes are brought into contact with the proteins of the present invention, thereby selecting the genes corresponding to the gene products that bind to the proteins of the present invention. There are no restrictions on the sample genes, but cDNA libraries prepared from the cells expected to express the proteins that bind to the proteins of the present invention are preferable. A specific example of the method utilizes the yeast 2 hybrid system (Fields, S. and Song, O., Nature 340:245-247 (1989)). Namely, one can express the proteins of the present invention within the yeast cells by fusing them with the SRF binding region, GAL4 binding region, or LexA binding region. One can then introduce the cDNA libraries prepared from the cells expected to express the proteins that bind to the proteins of the present invention into the above yeast cells so that the proteins are expressed in a form fused with the VP16, GAL4 transcription activation domain, or the *E. coli* B42 peptide. Finally, one can isolate the library-derived cDNA from the positive clones. (When a protein that binds to the protein of the present invention is expressed within the yeast cell, the binding between these proteins activates the reporter gene, enabling the detection of the positive clone.)

The vectors and expression libraries to be used in this system can be purchased from several sources (Clontech, MATCHMAKER Two-Hybrid System; Stratagene, HybriZAP II Two-Hybrid System). For the specific method, one can follow the manufacturer's manual. The genes encoding the proteins that bind to the proteins of the

present invention can be obtained directly by this method. In fact, the bindings between APC and hDLG (Matsumine, A., et al., Science 272:1020-1023 (1996)), between GRIP and the AMPA receptor (Dong, H., et al., Nature 386:279-284 (1997)), between Homer and the glutamate receptor (Brakeman, P. R., et al., Nature 386:284-288 (1997)), and between SRY and SIP-1 (Poulat, F., et al. J. Biol. Chem. 272:7167-7172 (1997)) were confirmed and the target proteins of the proteins having the PDZ domain were identified using this yeast 2 hybrid system.

It is also possible to screen the proteins by the "west-western blotting method" (Skolnik, E. Y., Margolis, B., Mohammadi, M., Lowenstein, E., Fischer, R., Drepps, A., Ullrich, A., and Schlessinger, J., Cloning of PI3 kinase-associated p85 utilizing a novel method for expression/ cloning of target proteins for receptor tyrosine kinases. Cell 65:83-90 (1991)). In this method, a cDNA library is prepared using a phage vector (such as λgt11 and ZAP) from the cells expected to express the proteins that bind to the proteins of the present invention (e.g., human umbilical vascular endothelial cells). The protein is then expressed on an LB-agarose, and the expressed proteins are fixed onto a filter with which the protein of the present invention that has been biotin-labeled or purified as a fusion protein with the GST protein is reacted. The plaques expressing the binding proteins are detected with streptavidin or an anti-GST antibody. It is then also possible to introduce the isolated genes from the above procedure into *E. coli* or other cells to express them and to prepare the proteins encoded by the genes.

It should be possible to determine the signal transduction pathways mediated by the protein-protein

interaction by using the proteins of the present invention to isolate and analyze their binding proteins and the genes encoding them. Furthermore, as the relationship between the signal transduction and diseases becomes clearer, it will be possible to develop pharmaceuticals targeted at the proteins of the present invention and the proteins that interact with them.

It is also expected that treatments using antisense DNA against the DNA encoding these proteins will become possible. In the present invention, "antisense DNA" refers to the DNA encoding the RNA that is complementary to the transcription product of the target gene, thereby employing the activity to suppress the expression of the target gene. Antisense DNA does not have to be perfectly complementary to the transcription product of the target gene, as long as it can effectively block the expression of the target gene. It preferably possesses 90% or more, and more preferably 95% or more, complementarity. The chain length of the antisense DNA is 15 nucleotides or more, preferably 100 nucleotides or more, and more preferably 500 nucleotides or more. Various modified antisense oligonucleotides are being utilized as antisense DNA. For example, phosphorothioates (S-oligos) are preferable in terms of stability and solubility. The methods for introducing antisense DNA include direct administration, lipofection, the HVJ method, and the HVJ-liposome method. It is also possible to perform the treatment with antisense RNA using vectors. In this case, the gene therapy is achieved by inserting the DNA of the present invention backwards into the vector used in the recombinant protein production in animal cells described above. The DNA is

then expressed within the body by introducing it through direct administration, lipofection, the HVJ method, the HVJ-liposome method, etc. It is also possible to employ the methods of gene introduction using virus vectors such as adeno-associated virus, Adenovirus, human herpes simplex virus, vaccinia virus, and Fowlpox virus, in order to express the antisense RNA within the body. Treatments using ribozymes, instead of antisense DNA, are also possible.

Brief Description of the Drawings

Figure 1. Sequence comparisons between "32-8-1" (top) and "AF00168" (bottom) are shown.

Figure 2. Sequence comparisons between "32-8-1" (top) and "AJ001319" (bottom) are shown.

Figure 3 Sequence comparisons between "32-8-1" (top) and "AJ001320" (bottom) are shown.

Figure 4. Continuation of Figure 3, sequence comparisons between "32-8-1" (top) and "AJ001320" (bottom) are shown.

Figure 5. Photograph of the electrophoresis showing the results of northern blot analysis of the "32-8-1 gene" is shown. The BamHI-XbaI fragment was used as the probe. "H" in the figure indicates the results with the Human Multiple Tissue Northern (MTN) Blot (Clontech #7760-1). The lanes are 1. Heart, 2. Brain, 3. Placenta, 4. Lung, 5. Liver, 6. Skeletal muscle, 7. Kidney, and 8. Pancreas. "H4" indicates the results with the Human Multiple Tissue Northern (MTN) Blot IV (Clontech #7766-1), and the lanes are 1. Spleen, 2. Thymus, 3. Prostate, 4. Testis, 5. Uterus, 6. Small intestine, 7. Colon, and 8. Peripheral Blood Leukocyte. "F2" indicates the results with the Human

Fetal Multiple Tissue Northern (MTN) Blot II (Clontech #7756-1), and the lanes are 1. Fetal brain, 2. Fetal lung, 3. Fetal liver, and 4. Fetal kidney.

Figure 6. Photograph of the electrophoresis showing the results of northern blot analysis of the "32-8-1 gene" is shown. The NdeI 1.2 kb-#1 probe was used. "H" in the figure indicates the results with the Human Multiple Tissue Northern (MTN) Blot (Clontech #7760-1), and the lanes are 1. Heart, 2. Brain, 3. Placenta, 4. Lung, 5. Liver, 6. Skeletal muscle, 7. Kidney, and 8. Pancreas. "H4" indicates the results with the Human Multiple Tissue Northern (MTN) Blot IV (Clontech #7766-1), and the lanes are 1. Spleen, 2. Thymus, 3. Prostate, 4. Testis, 5. Uterus, 6. Small intestine, 7. Colon, and 8. Peripheral Blood Leukocyte. "F2" indicates the results with the Human Fetal Multiple Tissue Northern (MTN) Blot II (Clontech #7756-1), and the lanes are 1. Fetal brain, 2. Fetal lung, 3. Fetal liver, and 4. Fetal kidney. "Mu" indicates the results with the Human Muscle Multiple Tissue Northern (MTN) Blot (Clontech #7765-1), and the lanes are 1. Skeletal muscle, 2. Uterus, 3. Colon, 4. Small intestine, 5. Bladder, 6. Heart, 7. Stomach, and 8. Prostate. "C" indicates the results with the Human Cancer Cell Line Multiple Tissue Northern (MTN) Blot (Clontech #7757-1), and the lanes are 1. Promyelocytic leukemia HL-60 cells, 2. HeLa S3 cells, 3. Chronic myelogenous leukemia K-562 cells, 4. Lymphoblastic leukemia MOLT-4 cells, 5. Burkitt's lymphoma Raji cells, 6. Colorectal adenocarcinoma SW480 cells, 7. Lung carcinoma A549 cells, and 8. Melanoma G361 cells.

Figure 7. Positional relationships among various clones isolated by the present inventors are presented.

These are the "32-8-1" cDNA clone; the heart cDNA derived "686-1-2" and "686-1-4" clones. The fetal liver cDNA derived "FL #5," "#12," and "#6" clones are also shown. The PDZ domains encoded by the 32-8-1 gene are indicated by circles. The translation initiation site at nucleotide 292 and the translation termination site at nucleotide 4410 are also indicated in the figure. The positions of the probes, NdeI 1.2 kb-#1 and BamHI-XbaI, are also shown.

Figure 8. PDZ domain sequences of the protein (SEQ ID NO: 1) encoded by the 32-8-1 gene are shown. The PDZ domain sequences that exist within the protein encoded by the 32-8-1 gene are aligned.

Figure 9. Four colonies of *E. coli* transformants expressing GST-PDZ56 were picked, and the expression was compared depending on the presence or absence of the isopropyl thiogalactoside (IPTG) induction. Transformants with pGST-2TK were used as a control. The samples from each clone were analyzed on a 10% to 20% SDS-polyacrylamide gel, with even-numbered lanes before the IPTG induction and odd-numbered lanes three hours after the IPTG induction. Lanes 2 and 3 correspond to the pGST-2TK transformants, and lanes 4 through 11 correspond to clone 1 through 4 of the *E. coli* transformants expressing GST-PDZ56. Lane 1 shows molecular weight markers. The bands corresponding to the induced expression of GST-PDZ56 are indicated with an arrow.

Figure 10. The same samples used in the experiment shown in Figure 9 were analyzed by western blot. Bands (indicated with an arrow) corresponding to the induced expression of the 55 kDa protein were detected with the anti-GST antibody. The bands near 30 kDa seen in the samples three hours after the IPTG induction are

interpreted to represent the degradation of the GST-PDZ56 protein.

Figure 11. The expression of GST-PDZ14 from the *E. coli* transformants three hours after the IPTG induction was analyzed by Coomassie blue staining. Lanes 2 and 6 correspond to the samples prior to the IPTG induction; lanes 3 through 6 correspond to clones 1, 2, 3, and 4 of the *E. coli* HB101 transformants; and lanes 8 through 11 correspond to clones 1, 2, 3, and 4 of the *E. coli* JM109 transformants, showing the results of GST-PDZ14 expression after the IPTG induction (arrow). Lane 1 shows molecular weight markers.

Figure 12. The purification process of PDZ56 is shown. Coomassie blue staining was used. Lane 1 shows molecular weight markers. Lane 2 corresponds to the culture media; lane 3, to the sonicated sample; lane 4, to the fraction unbound to the glutathione-Sepharose column; lanes 5 through 7, to the washes; and lanes 8 and 9, to the PDZ56 protein not containing the GST protein portion, which has come off the glutathione-Sepharose column after digestion by thrombin. Bands at approximately 30 kDa can be clearly seen (arrow indicates PDZ56). Lane 10 corresponds to the GST protein portion bound to the glutathione-Sepharose column, which was eluted after digestion by thrombin (arrow indicates GST). Lanes 11 and 12 show the GST-PDZ56 fusion protein that was eluted without thrombin digestion in a regular elution buffer containing glutathione (arrow indicates GST-PDZ56).

Figure 13. The results of western blotting performed with anti-GST antibody using a filter onto which the same samples used in the experiment shown in Figure 12 were blotted are shown. Comparing lanes 8 and 9 with lane 10

(arrow: GST) clearly shows that the 55kDa GST-PDZ56 fusion protein (arrow indicates GST-PDZ56) shown in lanes 11 and 12 has been cleaved by thrombin to yield only PDZ56 that does not contain the GST portion. Bands in lanes 8 and 9 of Figure 12 cannot be detected by the GST antibody used in Figure 13 because they do not contain GST.

Figure 14. The purification process of PDZ14, similar to that in Figure 9, is shown. Lane 1 shows molecular weight markers. Lane 2 corresponds to the culture media; lane 3, to the sonicated sample; lane 4, to the fraction unbound from the glutathione-Sepharose column; lanes 5 through 8, to the washes; and lanes 9, 10, and 11, to the PDZ14 protein not containing the GST protein portion, which came off the glutathione-Sepharose column after digestion by thrombin. Bands at 65 kDa can be clearly seen (arrow indicates PDZ14). However, degradation products of the PDZ14 protein were also detected at 28 kDa and 37 kDa (arrows indicate 37 kDa and 28 kDa).

Figure 15. Out of the Protein Medley (Clontech), the filters blotted with 100mg each of the cell lysates from human testis (T), skeletal muscle (Sk), liver (Lv), heart (H), and brain (B) were reacted with the antisera from the rabbits immunized with peptide 32-8-1-17, PDZ14, or PDZ56 for western blotting. The filters were reacted sequentially with the 5,000-fold diluted rabbit antiserum, the 1,000-fold diluted biotin-labeled anti-rabbit Ig antibody, and the 2,500-fold diluted horseradish peroxidase (HRP)-labeled streptavidin-biotin complex (Amersham). The results of detection by chemiluminescence of the proteins that react with the rabbit antisera are shown. In the liver tissue, the present inventors were able to detect a

band at around 130 kDa. This band is expected to have been derived from the 32-8-1 protein (arrow).

Figure 16. The results of an analysis of the tissue specificity of the 32-8-1 gene expression by RT-PCR are shown. The 24-types of first strand cDNAs used were 1. brain, 2. heart, 3. kidney, 4. liver, 5. lung, 6. pancreas, 7. placenta, 8. skeletal muscle, 9. colon, 10. ovary, 11. peripheral leukocyte, 12. prostate, 13, small intestine, 14. spleen, 15. testis, 16. thymus, 17. fetal brain, 18. fetal heart, 19. fetal kidney, 20. fetal liver, 21. fetal lung, 22. fetal skeletal muscle, 23. fetal spleen, and 24. fetal thymus. Single bands at 650 bp were detected in panel A, and three bands (750 bp, 850 bp, and 950 bp) were detected in panel B.

Figure 17. The comparisons among the sequences of FH750, FH850, and FH950 are shown.

Figure 18. The continuation of Figure 17 showing the comparisons among the sequences of FH750, FH850, and FH950 is shown.

Figure 19. A photograph of an electrophoresis presenting the results of detection of the 32-8-1b protein by western blotting is shown. Lanes 1 and 2 were detected with the antisera against the 32-8-1-17 peptide, and lanes 3 and 4 were detected with the antisera against PDZ56. Cell lysates from neuroblastoma cells SH-SY5Y (lanes 1 and 3) and the NT-N cells (lanes 2 and 4), which are neurons differentiated from NT-2 by the retinoic acid stimulation, were separated on an SDS-polyacrylamide gel. Bands that are expected to correspond to the 32-8-1b protein were detected with a size of 250 kDa or more.

Figure 20. Sequence comparisons between "32-8-1b" (top) and "AF00168" (bottom) are shown.

Figure 21. Sequence comparisons between "32-8-1b" (top) and "AJ001319" (bottom) are shown.

Figure 22. Sequence comparisons between "32-8-1b" (top) and "AJ001320" (bottom) are shown.

Figure 23. The continuation of Figure 22, which presents sequence comparisons between "32-8-1b" and "AJ001320," is shown.

Figure 24. The continuation of Figure 23, which presents sequence comparisons between "32-8-1b" and "AJ001320," is shown.

Figure 25. The sequences of the PDZ domains in the protein (SEQ ID NO: 83) encoded by the 32-8-1b gene are shown. The sequences of the PDZ domains that exist within the protein encoded by the 32-8-1b gene are aligned.

Figure 26. The positional relationships among the various clones isolated by the present inventors are shown. These are the "32-8-1" cDNA clone; the heart cDNA derived "686-1-2" clone, "686-1-4" clone, and "FH950" clone; the fetal liver cDNA derived "FL#5," "#12," and "#6" clones; and the brain derived "1.2 kb #33" clone and "D-2" clone are shown. The PDZ domains encoded by the "32-8-1b" gene are indicated by rectangles.

Best Mode for Implementing the Invention

Embodiments of the present invention are exemplified below. However, the present invention shall in no way be limited by these examples.

Example 1 Cloning of genes

(1) Differential display

The human umbilical vascular endothelial cells (HUVEC) were obtained from Morinaga Biochemistry Research Institute

and cultured by using the Normal Human Vascular Endothelial Cell Culturing kit (Catalog #680051). When the cells became subconfluent, 10 ng/ml Recombinant Human Tumor Necrosis Factor-α (TNFα, Catalog #300-01A, PEPROTECH Inc.) was added, and the cells were cultured for another 24 hours. The expressed genes were compared with those from the cells without the addition of TNFα. Cells were detached from the plate with trypsin-EDTA, precipitated by centrifugation at 1,000 rpm for 5 minutes, and washed once with PBS. The total RNA was then recovered by using an RNAeasy Total RNA kit (QIAGEN). Using 0.2 μg of the recovered total RNA, the present inventors synthesized cDNA by means of the H-T11G anchor primer. The conditions were based on those given in the manual for the RNAimage kit (GenHunter). Genes were randomly amplified using the TAKARA Taq polymerase through 40 cycles of polymerase chain reaction (PCR). Each cycle consisted of 94°C for 30 seconds, 40°C for 2 minutes, and 72°C for 30 seconds, for each of the eight kinds of arbitrary primers H-AP1 through H-AP8. The reaction mixture contained α-^{32}P dATP. The products were separated on sequencing gels, and those genes whose bands were intensified by the TNFα stimulation, that is, the genes whose mRNA expression was increased as compared to the case with no stimulation, were amplified again with the same conditions. The primer DNA was then removed from the reaction mixture using a Qiaquick Spin PCR Purification kit. The nucleotide sequence information of "DDEST32" shown in SEQ ID NO: 13 was obtained by analyzing the products with a Dye Terminator Cycle Sequencing FS Ready Reaction kit (Perkin Elmer, Catalog #402122) using the same primers used for amplification.

(2) Construction of cDNA library

A cDNA library was constructed using a ZAP-cDNA synthesis kit (Stratagene). A 10 x 1st strand buffer (5 µl), 3 µl of 1st strand methyl nucleotides mix, 2 µl of linker-primer (1.4 µg/µl), 1 ml of RNase Block ribonuclease inhibitor (40 U/µl), 10 µl of TNFα-stimulated HUVEC poly A^+ mRNA (0.5 µg/µl), and 24 µl of diethyl pyrocarbonate (DEPC)-treated water were gently mixed and allowed to stand at room temperature for 10 minutes. SuperScript II reverse transcriptase (5 µl, 200 U/µl, GIBCO-BRL) was mixed with the cDNA library. The mixture was incubated at 37°C for 40 minutes then at 45°C for 70 minutes. The reaction mixture was put on ice, and 20 µl of 10 x 2nd strand buffer, 6 µl of 2nd strand nucleotide mix, 115.9 µl of sterilized distilled water, RNase H (1.5 U/µl), and 11.1 µl of DNA polymerase I (9 U/µl) were mixed into 45 µ of the reacted mixture by vortexing, and the mixture was incubated at 16°C for 150 minutes. After the reaction, 23 µl of blunting dNTP mix and 2 µl of cloned Pfu DNA polymerase (2.5 U/µl) were added, and the mixture was incubated at 72°C for 30 minutes. The mixture was then sequentially extracted with 200 µl of phenol/chloroform, and with chloroform, and further precipitated by adding 20 µl of 3M sodium acetate and 400 µl of 100% ethanol. After overnight incubation at -20°C, the mixture was centrifuged at 15,000 rpm for 60 minutes (4°C), and the precipitate was washed with 500 µl of 70% ethanol and dried. The precipitate was dissolved in 9 µl of 0.4 µg/µl EcoRI adapter and incubated at 4°C for 45 minutes. 10 x ligase buffer (1 µl), 1 µl of 10 mM ATP, and 1 µl of T4 DNA ligase (4 U/µl) were then added to the above, and the ligation reaction was performed overnight at 8°C. The mixture was incubated at 70°C for

30 minutes to inactivate the enzyme, spun down to collect the solution on the bottom of the tube, and let sit for 5 minutes at room temperature. To the mixture were added 1 µl of 10 x ligase buffer, 2 µl of ATP, 6 µl of sterilized water, and 1 µl of T4 polynucleotide kinase (10 U/µl). The mixture was incubated at 37°C for 30 minutes then incubated again at 70°C for 30 minutes to inactivate the enzyme. XhoI buffer supplement (28 µl) and 3 µl of XhoI (40 U/µl) were added to the above, and the mixture was reacted at 37°C for 90 minutes. The mixture was cooled to room temperature, then 5 µl of 10 x STE buffer was added. The mixture was then applied to a Sephacryl S-500 column and eluted twice with 60 µl of 1 x STE buffer. Ethanol (120 ml) was then added to the mixture, and the mixture was allowed to stand at -20°C overnight. It was then centrifuged at 15,000 rpm for 60 minutes (4°C) to obtain the precipitate. The precipitate was washed with 200 µl of 80% ethanol and dried. It was then dissolved with 6 µl of sterilized water, and 2.5 µl of it was used for the ligation reaction with the vector. To 2.5 µl of the cDNA, 1 µl of Uni-ZAP XR vector (1 µg), 0.5 µl of 10 x ligase buffer, 0.5 µl of 10 mM ATP, and 0.5 µl of T4 DNA ligase (4 U/µl) were added and reacted at 12°C overnight. The ligation mixture (1 µl) was added to the GigapackIII Gold Packaging extract, mixed well, and incubated for two hours at room temperature. SM buffer (500 µl; 5.8 g NaCl, 2.0 g $MgSO_4$-$7H_2O$, 50 ml 1 M Tris-HCl (pH 7.5), and 5 ml 2% (w/v) gelatin, brought up to 1 L with deionized water) was added to the above, and after 20 µl of chloroform was added, it was gently mixed. The mixture was then centrifuged, and the supernatant was transferred to another tube and stored at 4°C. The phage titer was measured using 0.1 µl and 1 µl

of the packaging reaction. Since approximately 300 plaques were obtained from 0.1 µl, the titer was estimated to be 3,000 PFU (plaque-forming units) per microliter. XL1 Blue MRF' was used as the host *E. coli*. It was cultured in 20 ml LB/ 10 mM $MgSO_4$/ 0.2% maltose at 37°C for 6 hours, placed on ice for 5 minutes before the OD_{600} became 1.0, and centrifuged at 500 x g for 10 minutes. To resuspend the precipitated cells, 10 ml of 10 mM $MgSO_4$ was added, and cells were diluted with 10 mM $MgSO_4$ so that the OD_{600} became 0.5. The packaging reaction (17 µl) was added to 600 µl of the freshly prepared XL-1 Blue MRF', and incubated at 37°C for 15 minutes. NZY top agar (6.5 ml; made by adding 0.7% (w/v) agarose to the NZY medium and autoclaving it), which had been incubated at 45°C, was added to the above and plated onto NZY agar plates. The plates were prepared as follows. NaCl (5 g), $MgSO_4$-$7H_2O$ (2.0 g), yeast extracts (5 g), NZ amines (10 g), and agar (15 g) were dissolved in deionized water to make the total volume 1 L. The solution pH was adjusted with NaOH to 7.5, after which the solution was autoclaved and poured into sterilized culture plates. After culturing at 37°C for six hours, the plaques were transferred onto a Hybond N^+ filter (Amersham, RPN203B) by placing the filter on the plate, denatured with 1.5 M NaCl-0.5 M NaOH for 7 minutes, neutralized by treating with 1.5 M NaCl-0.5 M Tris-HCl (pH 7.2)/ 1 mM EDTA for 5 minutes, and finally rinsed with 2 x SSC. After the filter was dried, the plaques were fixed onto the filter by StrataLinker (Stratagene).

(3) Screening of the cDNA library

The "DDEST32" DNA fragment was isolated on a 2% agarose gel, and recovered from an agarose gel slice with a

QIAEX II gel extraction kit (QIAGEN). The fragment was labeled by random labeling so it could be used as the probe. Using a Megaprime kit (Amersham, RPN1607), 5 µl of primer solution was added to 25 ng of the probe DNA, and incubated at 95°C for 5 minutes. After the solution was incubated at room temperature, 10 µl of labeling buffer, 18 µl of water, 5 µl of α^{32}P dCTP (-3000ci/mmol; Amersham), and 2 µl of Klenow fragment were added to it, and the mixed solution was incubated at 37°C for 30 minutes. The reaction was stopped by adding 2 µl of 0.5 M EDTA, and the free α-^{32}P dCTP was removed with a Pharmacia ProbeQuant G-50 column. After prehybridization at 60°C in the Rapid hybri buffer (Amersham, RPN1636), the labeled probe was heat-denatured at 95°C, rapidly chilled on ice, and added to the hybridization buffer. Hybridization was then performed by shaking at 60°C for two hours. The probe was used at a concentration of 2 x 10^6 cpm/ml. The filter was washed three times in 2 x SSC/ 0.05% SDS at room temperature for ten minutes each, and twice more in 0.1 x SSC/ 0.1% SDS at 60°C for 20 minutes each. The phage collected from positive plaques was diluted in SM buffer and plated onto 10-cm plates so that approximately 100 plaques were formed per plate. The secondary and tertiary screenings were performed similarly. As a result, clone "#32-8-1" was obtained as the positive clone. The gene that had been cloned in the Uni-ZAP vector was recovered as ordinary plasmid DNA by the *in vivo* excision method.

Example 2 Sequence determination of the "32-8-1" gene

(1) Preparation of the cDNA library for RACE

The cDNA for RACE was synthesized using a Marathon cDNA amplification kit (Clontech). The total RNA (1 µg)

obtained from the TNFα-stimulated HUVEC cells was used for the experiment. Oligo dT primer (1 µl, 10 µM) was added to the above, the total volume was brought to 5 µl, and the mixture was incubated at 70°C for 2 minutes and then placed on ice for 2 minutes. Two microliters of 5 x 1st strand buffer, 1 µl of 10 mM dNTP mix, and 1 µl of 100 U/µl MMLV reverse transcriptase were added to the above, and the total volume was made 10 µl. The mixture was then incubated at 42°C for 1 hour to synthesize the first strand cDNA. Sixteen microliters of 5 x 2nd strand buffer, 1.6 µl of 10 mM dNTP mix, and 4 µl of 20 x 2nd strand enzyme cocktail were next added to the mixture, the total volume was adjusted to 80 µl with water, and the mixture was incubated at 16°C for 90 minutes. T4 DNA polymerase (2 µl, 5 U/µl) was then added, and the reaction was performed at 16°C for 45 minutes. After 4 µl of 20 x EDTA/ glycogen was added to the mixture, it was deproteinized with equal volumes of phenol/chloroform, and isoamyl alcohol/chloroform.

Ethanol precipitation was done with 35 µl of 4 M ammonium acetate and 263 µl of 95% ethanol, and the precipitate was washed with 80% ethanol and spontaneously dried for 10 minutes. The dried precipitate was dissolved in 10 µl of deionized water, and 7.5 µl was used for the adapter ligation reaction. Marathon cDNA adapter (3 µl, 10 µM), 3 µl of 5 x DNA ligation buffer, and 1.5 µl of T4 DNA ligase (1 U/µl) were added to the above and reacted overnight at 16°C. The enzyme was inactivated by incubation at 70°C for 5 minutes, and the total volume was adjusted to 150 µl by using 135 µl of Tricine-EDTA buffer contained in the kit.

(2) cDNA cloning by RACE and sequence determination

Clone #32-8-1 was subcloned by utilizing the restriction enzyme recognition sites within the gene (PstI, XbaI, BamHI, and EcoRI), and the nucleotide sequence was determined by the cycle sequence method using a Dye Terminator Cycle Sequencing FS Ready Reaction kit (Perkin Elmer, Catalog #402122).

The sequences of the primers used are shown in Table 1. "C" indicates a primer for the complementary DNA strand.

Table 1

Primer #		DNA sequence	SEQ ID NO:
106	C	CTCCCCATCCCTCGTCCACC	14
XE	C	CTCTGACTCTGACTGACTGG	15
EX		ATGAGTTTGGTTACAGCTGG	16
402		TCAGAGAGCGTTATGGAACC	17
XER		AGTCTTGCTGGGAACAAAGA	18
801		ACTGTTACTACTTCTGATGC	19
1192-1161		TCTGATGGTCCCACAGTCTG	20
1282	C	GTTGTTTCGCAGCCAGGGAT	21
1524		CTGAGCATCGTTGGGGGTTC	22
1449	C	CCTCATCTCTGTAGAGTGTC	23
1683		TGTTAGCCCCCTCACTAAGG	24
1803		GCTATGTGCTAGGAAATACG	25
2116		TAGGGAGAAGGATCAGAGCG	26
607-93		ACAGATTTCTGACTCACTGG	27
128		TGGAAATAGGCATTCTTCAG	28
607-462		ATACAAAGACGGTCTAATCC	29
2920	C	CCGCTTTCCCATCTTTAGAAAC	30
3121		TATCTCGTGTGGAAGATGTG	31
2266-107	C	ACATAAATGTTGCTATCACC	32
3361		TGCCACTTAGTAGCCGAGTG	33
3615		GCATTGCATTACAGTTGAGC	34
1301	C	TCCTCCTTTGACAATGTCTG	35
BXR	C	CATTTCGACTGTTCTTAATC	36
XB	C	TCAGTGGATGTGCCACAGAT	37
4221	C	CAGTAGGTTAACTGCTTCGG	38
BX		AGTTCCAGTCTTTCTTTCGG	39
4335		TTTCTTTCACTGGGCTGAAGTC	40
XBR		CCTCTGAAGACGGACGTCTG	41

Accordingly, a nucleotide sequence of 5,146 bp was determined. When the first G of the EcoRI recognition site was counted as nucleotide 1, the PDZ domain started at nucleotide 468. A stop codon immediately followed three repeated stretches of approximately 80 amino acids. The sequence in the 3′ region of the gene also contained three PDZ domains at a distance of approximately 2 kb from the stop codon described above. (An experiment conducted later revealed that clone #32-8-1 contains a sequence of approximately 2 kb. This sequence has been derived from an intron, transcribed and inserted, thereby introducing the stop codon immediately after the first three PDZ domains.)

Therefore, the present inventors performed 5′ Rapid Amplification of cDNA Ends (RACE) starting from the position of the three PDZ domains found in the latter half. Using 5 µl of the cDNA described above, 5′ RACE was performed according to the manual contained in the kit. The reaction mixture consisted of 5 µl of cDNA, 5 µl of 10 x Advantage™ KlenTaq buffer (which came with the kit), 4 µl of 2.5 mM dNTP, 1 µl of 10 µM AP1 primer (CCATCCTAATACGACTCACTATAGGGC (SEQ ID NO: 42)), 1 µl of 10 µM 32-8-1 5′ RACE primer #22(TTGGGGTGGGGAGAGGAGGTAGATTGC (SEQ ID NO: 43)), 1 µl of Advantage™ KlenTaq polymerase mix (Toyobo, CLK8417-1), and 33 µl of deionized water to make the total 50 µl. PCR reaction was performed using a Perkin Elmer Thermal Cycler 2400. A reaction consisting of 94°C for 1 minute, five cycles of 94°C for 5 seconds and 72°C for 2 minutes, five cycles of 94°C for 5 seconds and 70°C for 2 minutes, followed by 25 cycles of 94°C for 5 seconds and 68°C for 2 minutes did not produce clearly detectable bands. By performing nested PCR under the same conditions, the present inventors were able to obtain a band of

approximately 1.8 kb. Here the AP2 primer (ACTCACTATAGGGCTCGAGCGGC (SEQ ID NO: 44)) and 32-8-1 5′ RACE primer #1034 (GCACATCACCAAGTGGGCTGCCTACTC (SEQ ID NO: 45)) were used as primers, and 5 µl of the 50-fold dilution of the initial PCR product was used. Also, the original 25 cycles of 94°C for 5 seconds and 68°C for 2 minutes was reduced to 15 cycles. As a result, cDNA clone "32-8-1/5R3," which does not contain the 2 kb gap, was obtained.

Next, the present inventors determined the sequence of clone 32-8-1/5R3. The sequences of the primers used for the sequence determination of 32-8-1/5R3 are shown in Table 2. "C" indicates a primer for the complementary DNA strand.

Table 2

Primer #		DNA sequence	SEQ ID NO:
EX		ATGAGTTTGGTTACAGCTGG	46
456	C	AATCTAATGCAGCTCGCCTG	47
XER		AGTCTTGCTGGGAACAAAGA	48
678	C	TCACTTTAGAAGGGGCACAT	49
801		ACTGTTACTACTTCTGATGC	50
1192-1161		TCTGATGGTCCCACAGTCTG	51
1282	C	GTTGTTTCGCAGCCAGGGAT	52
1524		CTGAGCATCGTTGGGGGTTC	53
1449	C	CCTCATCTCTGTAGAGTGTC	54
2116		TAGGGAGAAGGATCAGAGCG	55
1301	C	TCCTCCTTTGACAATGTCTG	56
839		TTTCATCATCTACAGCCAGT	57
1389		TGACACCCTCACTATTGAGC	58

The nucleotide sequence of 2,819 bp, which was determined by combining the sequences of clones #32-8-1 and 32-8-1/5R3, is shown in SEQ ID NO: 59.

Example 3 Cloning of a cDNA clone corresponding to the 5′ upstream region of the 32-8-1/5R3 cDNA clone by RACE

The present inventors attempted to isolate the upstream cDNA located 5′ to the 32-8-1/5R3 clone by the 5′ Rapid Amplification of cDNA Ends (RACE) method. A human heart cDNA library and a human fetal liver cDNA library were used as cDNA sources. Two clones, 2.8 kb and 1.2 kb in size, were obtained from the human heart cDNA library. One 1.1 kb clone was obtained from the human fetal liver cDNA library. The cloning procedure is described below.

The present inventors used cDNA Library Human Heart (Takara Shuzo, Catalog #9604) for the human heart cDNA library. The XL1 Blue-MRF′ *E. coli* cells transformed with the plasmid DNA containing the cDNA inserted into the pAP3neo vector (Genbank Accession No.AB003468) were cultured by the usual method, the plasmid DNA was recovered by the alkaline method, and the cDNA clone containing the 5′ upstream region was obtained by PCR using 10 ng of the plasmid DNA as the template. The reaction mixture consisted of 10 ng of the cDNA, 5 µl of 10 x Advantage™ KlenTaq buffer (which came with the kit), 4 µl of 2.5 mM dNTP, 1 µl of 10 µM AP3neo5′ primer (which came with the kit; 5′-GCCCTTAGGACGCGTAATACGACTC-3′ (SEQ ID NO: 60)), 1 µl of 10 µM 32-8-1 5′ RACE primer #686 (5′-AGCCAGTATCTGATCTCCGACTTTG-3′ (SEQ ID NO: 61)), and 1 µl of Advantage™ KlenTaq polymerase mix (Toyobo, CLK8417-1). These were mixed with deionized water to make the total 50 µl. PCR reaction was performed using a Perkin Elmer Thermal Cycler 2400. A reaction consisting of 94°C for 1 minute, 5 cycles of 94°C for 5 seconds and 72°C for 4 minutes, and 5 cycles of 94°C for 5 seconds and 70°C for 4 minutes, followed by 25 cycles of 94°C for 5 seconds and

68°C for 4 minutes, yielded the bands of 2.8 kb and 1.2 kb. The products were separated on a 0.8% agarose gel. The corresponding bands were excised and purified with the QIAquick gel extraction kit (QIAGEN, 28706) and were subjected to TA cloning according to the manual for the pGEM-T Vector System I (Promega, A3600). The present inventors designated the two clones as 686-1-4 (2.8 kb) and 686-1-2 (1.2 kb). The sequence of clone 686-1-2 is contained in that of 686-1-4 (sequence 686-1-4), and ranges from nucleotide 1585 to nucleotide 2793 of SEQ ID NO: 3 (Figure 7).

The present inventors performed 5' RACE using Marathon Ready human fetal liver cDNA (Clontech) as the human fetal liver cDNA library. The reaction mixture consisted of 5 µl of the cDNA, 5 µl of 10 x Advantage™ KlenTaq buffer (which came with the kit), 4 µl of 2.5 mM dNTP, 1 µl of 10 µM AP1 primer (which came with the kit: 5'-CCATCCTAATACGACTCACTATAGGGC-3' (SEQ ID NO: 42)), 1 µl of 10 µM 32-8-1 5' RACE primer #686 (5'-AGCCAGTATCTGATCTCCGACTTTG-3' (SEQ ID NO: 61)), and 1 ml of Advantage™ KlenTaq polymerase mix (Toyobo, CLK8417-1). These were mixed with 33 µl of deionized water to make the total 50 µl. PCR reaction was performed using a Perkin Elmer Thermal Cycler 2400. A reaction consisting of 94°C for 1 minute, 5 cycles of 94°C for 5 seconds and 72°C for 6 minutes, 5 cycles of 94°C for 5 seconds and 70°C for 6 minutes, and 25 cycles of 94°C for 5 seconds and 68°C for 6 minutes did not produce clearly detectable bands. The reaction mixture was then diluted 50 fold, 5 µml of which was mixed with 5 µml of 10 x Advantage™ KlenTaq buffer (which came with the kit), 4 µl of 2.5 mM dNTP, 1 µl of 10 µM AP2 primer (which came with the kit;

5'- ACTCACTATAGGGCTCGAGCGGC-3 (SEQ ID NO: 44)), 1 µl of 10 µM 32-8-1 5' RACE nested primer #FLN (5'-ATTTTCACTTTAGAAGGGGCACAT-3'(SEQ ID NO: 62)), 1 µl of Advantage™ KlenTaq polymerase mix (Toyobo, CLK8417-1), and 33 µl of deionized water to make the total 50 µl. Nested PCR was performed at 94°C for 1 minute, 5 cycles of 94°C for 5 seconds and 72°C for 6 minutes, 5 cycles of 94°C for 5 seconds and 70°C for 6 minutes, and 15 cycles of 94°C for 5 seconds and 68°C for 6 minutes, which produced a band of approximately 1.1 kb. The products were separated on a 0.8% agarose gel. The corresponding bands were then excised and purified with a QIAquick gel extraction kit (QIAGEN, 28706) and were subjected to TA cloning according to the manual for the pGEM-T Vector System I (Promega, A3600). Three different clones were thus obtained and designated HFL#5, HFL#12, and HFL#6. HFL#5 and HFL#12 started from nucleotide 1357 of SEQ ID NO: 3, while HFL#6 started from nucleotide 1377 of SEQ ID NO: 3. Of course, all three contained the sequence up to that of primer #FLN, which was used in the RACE (Figure 7).

The nucleotide sequences were determined as described above, by means of the cycle sequence method using a Dye Terminator Cycle Sequencing FS Ready Reaction kit (Perkin Elmer, Catalog #402122). The combined sequence of the previously determined one and the newly determined one is shown in SEQ ID NO: 3. Figure 8 shows the sequences of nine PDZ domains aligned. The primers used for the cycle sequencing method are listed in Table 3.

Table 3

Primer #	DNA sequence	SEQ ID NO:
686A	GGCATAACTTTACTTACTTG	63
686B	ATCTACTAAGTCAGCATCAT	64
686C	ATTTGCAGGTGTGTAGTCAT	65
686D	TTCCTTCTGTGCTACCCGAT	66
686E	GGACTATCTTCCAGAACATG	67

Example 4 Search for proteins having homology to the protein encoded by the "38-2-1" gene

The BLASTN search and the BLASTP search detected "Mus musculus 90RF binding protein 1 (9BP-1) mRNA, partial cds." (LOCUS: MMAF000168, ACCESSION: AF000168) that consists of 2703 bp as a gene having homology to the "32-8-1" gene. This gene was recorded toGenBank on 18 MAY 1997. The amino acid sequence of the protein encoded by the "32-8-1" gene (the sequence after amino acid 847 of SEQ ID NO: 1) and that of AF000168 are aligned and shown in Figure 1. In the figure, the amino acid 847 of SEQ ID NO: 1 was regarded as the "first" amino acid, and comparisons are shown with the amino acid sequence thereafter.

In addition, "Rattus norvegius mRNA for multi PDZ domain protein" (LOCUS: RNMUPP1, ACCESSION: AJ001320) consisting of 7516 bp, and "Homo sapiens mRNA for multi PDZ domain protein" (LOCUS: HSMUPP1, ACCESSION: AJ001319) consisting of 1768 bp were detected as genes having homology. These genes were registered on 26 MAR 1998. The amino acid sequence of the protein encoded by the "32-8-1" gene (the sequence after amino acid 921 of SEQ ID NO: 1) and that of AJ001319 are aligned and shown in Figure 2. The amino acid sequence of the protein encoded

by the "32-8-1" gene (the sequence of SEQ ID NO: 1) and that of AJ001320 are aligned and shown in Figures 3 and 4.

Example 5 Analysis of tissue specificity of expression by northern blotting

Clontech Human Multiple Tissue Northern (MTN) Blot (Catalog #7760-1), Human MTN Blot IV(Catalog #7766-1), Human Fetal MTN Blot II (#7756-1), Human Muscle MTN Blot (#7765-1) and Human Cancer Cell Line MTN Blot (#7757-1) were used to analyze the tissue specificity of gene expression. Northern blot was performed according to the standard method, using the BamHI-XbaI fragment (from position 3709 to position 4337 of SEQ ID NO: 3) as the probe (see Figure 7 for the position of the probe), and 25 ng of the DNA fragment was labeled with α-^{32}P dCTP using a Megaprime DNA labeling kit (Amersham, Catalog RPN1607). These MTN Blots were prehybridized in 5 ml of the ExpressHyb hybridization solution (Clontech, Catalog #8015-2) at 68°C for 30 minutes, and then hybridized with 1 x 10^7 cpm of the labeled probe also in 5 ml of the ExpressHyb hybridization solution (2 x 10^6 cpm/ ml) at 68°C for 2 hours. The filters were washed three times in 2 x SSC (0.3 M NaCl, 0.03 M sodium citrate (pH 7.0))/ 0.05% SDS at room temperature for 10 minutes each, washed twice more in 0.1 x SSC/ 0.1% SDS at 50°C for 15 minutes each, exposed on FUJI imaging plates overnight, and analyzed by a FUJI BAS2000. As shown in Figure 5, strong expression of the approximately 8 kb transcription product was detected in the heart, placenta, skeletal muscle, fetal brain, fetal lung, fetal kidney, small intestine, bladder, stomach, prostate, HeLa S3 cells, lung cancer A549 cells, and melanoma G361 cells. However, the expression was either

absent or weak in the lung, lymphoid tissues (spleen and thymus), and cell lines (lanes 1, 3, 4, 5, and 6 of blot C). In the heart, liver, kidney, and fetal liver, a 5.5 kb transcription product was expressed.

Similarly, northern blot analysis was performed using the NdeI 1.2 kb-#1 probe (from position 1 to position 1091 of SEQ ID NO: 3) (see Figure 7 for the position of the probe). However, the band corresponding to the 5.5 kb transcription product was not detected (Figure 6). Considering this and the fact that the cDNAs cloned by 5′ RACE from the fetal liver only contained the 5′ sequences 1,357 and 1,377 nucleotides downstream from the 5′ end of the transcription product expressed in the heart (Figure 7), it can be deduced that the difference of the transcription initiation sites in the heart and liver caused the difference in the lengths of the transcription products. Therefore, the peptide encoded by the 32-8-1 gene that is expressed in the liver is expected to start with the first methionine encoded by the ATG codon beginning with the 1396th nucleotide. This results in the transcription product from the liver consisting of 1,005 amino acids, compared with that from the heart consisting of 1,373 amino acids. Consequently, it does not contain PDZ domain E and is shorter by 368 amino acids. Although the biological significance of not having PDZ domain E is unclear at present, it is highly possible that this protein, by lacking this portion, is involved in a different signal regulation in the liver cells than in the other tissues since PDZ domains are important for protein-protein interactions

Example 6 Expression of the 32-8-1 protein in *E. coli*

(1) Construction of the expression vector

In order to express the 32-8-1 protein in *E. coli* as a fusion protein with the glutathione-S-transferase (GST) protein, part of the 32-8-1 gene was ligated to the carboxyl terminus of the GST gene in Pharmacia's pGEX-2TK (Genbank Accession U13851). The vector was constructed based on the method of W. Dietmaier et al. for the di-/tri-nucleotide sticky end cloning described in the PCR Application Manual (Boehringer Mannheim). pGEX-2TK (1 µg) was reacted in a mixture of 2 ml of 10 x High buffer and 20 units each of restriction enzymes EcoRI and BamHI in a total volume of 20 µl at 37°C for 3 hours. Proteins were removed by using a QIAquick column (QIAGEN) according to the manual, and the purified DNA was eluted with 30 µl of distilled water. 10 x Klenow buffer (3 µl; 100 mM Tris-HCl (pH 7.5), 70 mM $MgCl_2$, 1 mM DTT), which comes with Takara's Klenow enzyme, and 1.5 µl of 2 mM dGTP were mixed with 27 µl of the above. Four units of Klenow enzyme were then added, and the reaction was allowed to proceed at room temperature for 15 minutes. After the enzyme was inactivated by heating at 75°C for 15 minutes, the DNA was purified by deproteinizing with a QIAquick column (QIAGEN) according to the manual.

The region of the 32-8-1 gene to be expressed, which encodes amino acids 1112 to 1373, was amplified by PCR using 50 ng of #32-8-1 DNA as the template. The amplification reaction was done by adding 5 µl of 10 x Reaction buffer #1 for KOD DNA polymerase (Toyobo), 5 µl each of 10 µM primer 502-508 (5'-ATCGGGTCCATTCCATTCAGAGAGG-3' (SEQ ID NO: 68)) and 10 µM primer 758-763E

(5'-AATTGTCAAGAGAGAACCATCAAAGTGG-3'(SEQ ID NO: 69)), 4 µl of 2.5 mM dNTP, 2 µl of 25 mM $MgCl_2$, and 27 µl of sterilized water. 2.5 µl of KOD DNA polymerase was then mixed into the solution, which was then incubated at 94°C for 2 minutes and subjected to 25 cycles of 98°C for 15 seconds, 65°C for 2 seconds, and 74°C for 30 seconds. Using the QIAquick PCR purification kit, the 798 bp PCR product was purified according to the manual. The purified PCR fragment (2 µl) was mixed with 7 µl of the Boehringer's 5 x T4 DNA polymerase buffer (330 mM Tris-acetate, pH 8.0; 660 mM potassium acetate; 100 mM magnesium acetate; and 5 mM DTT), 1.5 µl of 2 mM dCTP, and 21.5 µl of sterilized water. Three units of T4 DNA polymerase were then added, and the solution was reacted at 12°C for 30 minutes. The present inventors inactivated the enzyme by incubation at 80°C for 15 minutes and purified the mixture with the QIAquick PCR purification kit according to the manual. The pGEX-2TK plasmid, which had been digested with restriction enzymes EcoRI and BamHI and modified with Klenow, and the T4 polymerase-treated PCR product were ligated by one unit of T4 DNA ligase (Promega) using the attached buffer (30 mM Tris-HCl (pH 7.8), 10 mM $MgCl_2$, 10 mM DTT, and 1 mM ATP) at 15°C overnight. The reaction mixture was then used to transform *E. coli* DH5 alpha. The recombinant protein expressed by the transformant was designated GST-PDZ56.

Similarly, a PCR product encoding the amino acids from position 611 to position 1142 of SEQ ID NO: 1 was prepared by the above described method with primer 1-7 (5'-ATCGATGGGTAGTAATCACACACAG-3' (SEQ ID NO: 70)) and primer 527-532E (5'-AATTGCTATACTGGATCCAGAGAGTGG-3' (SEQ ID NO: 71)), using clone 32-8-1/5R3 as the template. The preparation was treated with T4 polymerase under the same

conditions as before, purified with the EcoRI and BamHI-digested and Klenow-treated pGEX-2TK, and ligated. The reaction mixture was used to transform *E. coli* DH5 alpha. The recombinant protein expressed by the transformant was designated GST-PDZ14.

The *E. coli* transformants that express GST-PDZ56 were selected by the following method. Four colonies of the *E. coli* transformants obtained from the above were shake-cultured at 37°C overnight in 2 ml of the LB medium (5 g of Bacto-yeast extract (DIFCO), 10 g of Bacto-trypton (DIFCO), and 10 g of NaCl made to 1 L by dissolving them in distilled water) containing 100 µg/ml ampicillin. The solution was then diluted 100 fold in the medium of the same composition, and isopropyl thiogalactoside (IPTG) was added to a final concentration of 0.1 mM. The solution was then shake-cultured at 37°C for 3 hours. A 100 µl sample was precipitated by centrifugation at 15,000 rpm for 10 seconds and analyzed on a 10% to 20% SDS-polyacrylamide gel. The subsequent Coomassie staining easily detected the IPTG-induced expression of the approximately 55 kDa GST fusion protein from every transformant (Figure 9). Furthermore, western blotting with an anti-GST antibody also confirmed the induced expression of the 55 kDa protein band (Figure 10). For detection, the proteins in the samples separated on the 10% to 20% SDS-polyacrylamide gel were transferred onto Immobilon-P (Millipore) using a Semidry blotter (Bio-Rad) according to the methods described in the manual. The filter was then blocked at 4°C overnight with 5% skim milk (DIFCO), 2.5% bovine serum albumin (Sigma, A5940), and T-TBS (20 mM Tris-HCl (pH 7.5), 150 mM NaCl, and 0.05% Tween 20). It was next reacted at room temperature for 1 hour with the anti-sheep GST

antibody (Pharmacia) diluted 1,000 fold in the antibody dilution buffer (1% skim milk, 0.5% bovine serum albumin, T-TBS), then reacted at room temperature for 1 hour with the alkaline phosphatase-labeled anti-sheep IgG antibody diluted 1,000 fold in the antibody dilution buffer. Finally, the protein was detected by a GST Detection Module (Pharmacia).

The GST-PDZ14 was similarly expressed. However, *E. coli* HB101 and JM109 were used as hosts because *E.coli* DH5 did not produce an efficient IPTG-induced expression. The results shown in Figure 11 indicate that *E. coli* HB101 did not produce very large amounts of expression products, but that the GST-PDZ14-derived band near 90 kDa was highly induced in *E.coli* JM109. *E. coli* JM109 was subsequently used to express and purify the fusion protein.

(2) Expression and purification of the GST 32-8-1 fusion protein

The present inventors followed the method for preparing fusion proteins described on page 217 of the Supplement to Jikken Igaku (Experimental Medicine) "Shin Idenshi Kogaku Handbook (New Genetic Engineering Handbook) edited by Masami Muramatsu, et. al." published by Yohdosha to express and purify the GST fusion proteins. GST-PDZ14 and GST-PDZ56 were each cultured at 37°C for 1 hour in 2 L of LB medium to which IPTG was added to achieve a final concentration of 0.1 mM, then shake-cultured at 25°C for 5 hours. The cells were collected at 7,000 rpm for 10 minutes, resuspended in a sonication buffer consisting of PBS and 1% Triton X-100, and sonicated 1 minute for five times while chilling. The supernatant was obtained by centrifugation at 10,000 rpm for 15 minutes. It was then

applied onto a glutathione-Sepharose column, washed well with PBS, and purified with the GST Purification Module elution buffer (Pharmacia Biotech).

The 32-8-1 gene was inserted into the multi-cloning site of the pGEX-2TK expression vector (Pharmacia). This vector has a region encording the string of amino acids "Leu-Val-Pro-Arg-Gly-Ser" recognized by thrombin protease in frame after GST protein gene, so the GST protein portion can be separated from GST-32-8-1 fusion protein by applying the thrombin protease that recognizes this sequence and digesting the protein. This is useful for preparing antibodies against the protein encoded by the 32-8-1 gene (the 32-8-1 protein). Because the glutathione-Sepharose column binds to the GST protein, it was possible to purify the PDZ14 and PDZ56 portions only as the fractions not binding to the glutathione-Sepharose (Figures 12, 13, and 14) by applying the protein solution that had been digested with the thrombin protease onto the glutathione-Sepharose column. The 55 kDa GST-PDZ56 protein bands seen in Figure 12 (lanes 11 and 12) were digested by thrombin into the 25 kDa GST protein and the 30 kDa PDZ56 protein (lane 10). Furthermore, the results of western blotting using the anti-GST antibody indicated that the anti-GST antibody reacted only with the 55 kDa and 25 kDa proteins, both of which contained the GST protein (Figure 13). Together, these confirmed that the PDZ56 protein portion was cut off as the 30 kDa band (lanes 8 and 9). Similarly to GST-PDZ14, the 90 kDa GST-PDZ14 can be separated by thrombin digestion into the 25 kDa GST protein and the 65 kDa PDZ14 protein portion, as shown in Figure 14. Therefore, the protein was purified according to the following procedure. The present inventors used the method

described in the Supplement to Jikken Igaku (Experimental Medicine) "Shin Idenshi Kogaku Handbook (New Genetic Engineering Handbook) edited by Masami Muramatsu, et. al" published by Yohdosha to culture *E. coli* cells. They then used the supernatant of the sonicated cells to digest the proteins by thrombin. The detailed method followed the procedure described under Thrombin Cleavage on page 16 of the GST Gene Fusion System (Pharmacia). They next added 10 µl (10 cleavage units) of thrombin per 1 mg of the fusion protein and incubated the mixture at room temperature for 16 hours to separate the PDZ14 protein or the PDZ56 protein portion from the GST portion. By letting the cleaved GST protein portion bind to the glutathione-Sepharose column (Pharmacia), they recovered 0.56 mg of the PDZ14 or 3.5 mg of the PDZ56 protein portion as the flow-through from the column.

(3) Preparation of polyclonal antibodies using the antigens expressed in *E. coli*

The present inventors obtained polyclonal antibodies by immunizing two rabbits each with the purified PDZ14 or PDZ56 antigen. The initial immunization was done by subcutaneously injecting 0.5 mg of PDZ56 or 0.22 mg of PDZ14 bound with the carrier protein per animal as an antigen emulsion mixed with an equal amount of Freund's complete adjuvant (FCA) by the standard method. Booster injections of 0.25 mg of PDZ56 or PDZ14 were given subcutaneously as an antigen emulsion mixed with an equal amount of Freund's incomplete adjuvant (FICA) three times at two-week intervals. The proteins used as antigens were separated by SDS-PAGE and transferred onto a PVDF membrane

(Immobilon-P, Millipore); the reactivity was confirmed by western blotting.

(4) Preparation of polyclonal antibodies using a peptide

Iwaki Glass synthesized Peptide 32-8-1-17 (SEQ ID NO: 72) consisting of 21 amino acids under contract. The Keyhole limpet hemocyanin (KLH) protein was coupled to the peptide as a carrier protein by the Sulfo-MBS method, and two rabbits were immunized with the product. The initial immunization was done by subcutaneously injecting 0.4 mg of the 32-8-1-17 peptide bound with the carrier protein per animal as an antigen emulsion mixed with an equal amount of Freund's complete adjuvant (FCA) by the standard method. The second through the fifth immunizations were given at two-week intervals by subcutaneously injecting 0.2 mg of the 32-8-1-17 peptide bound with the carrier protein as an antigen emulsion mixed with an equal amount of Freund's incomplete adjuvant (FICA). The antibody titers were measured using an ELISA plate coated with the 32-8-1-17 peptide; the antisera were obtained when the titer had risen sufficiently.

(5) Reactivity of the polyclonal antibodies

Antisera were obtained by immunizing the rabbits with peptide 32-8-1-17 or with PDZ14 or PDZ56 protein expressed as a GST-fusion protein and then digested with thrombin to retain only the 32-8-1 gene product. The reactivity of the antisera was detected by western blotting using Protein Medley manufactured by Clontech. More specifically, 100 µg each of the cell lysates of the tissues from the human Testis (T), Skeletal Muscle (Sk), Liver (Lv), Heart (H), and Brain (B) of the Protein Medley manufactured by

Clontech was separated on a 10% to 20% SDS-polyacrylamide gel. The cell lysates were then transferred onto Immobilon-P (Millipore) using the Semidry blotter (Bio-Rad) according to the methods described in the manual. The filter was then blocked at 4°C overnight with 5% skim milk (DIFCO), 2.5% bovine serum albumin (Sigma, A5940), and T-TBS (20 mM Tris-HCl (pH 7.5), 150 mM NaCl, and 0.05% Tween 20). The filter was next reacted at room temperature for 1 hour with the individual rabbit antisera diluted 5,000 fold in the antibody dilution buffer (1% skim milk, 0.5% bovine serum albumin, and T-TBS). It was then reacted at room temperature for 1 hour with the biotin-labeled anti-rabbit Ig diluted 1,000 fold in the antibody dilution buffer. Finally, the filter was further reacted at room temperature for 15 minutes with the horseradish peroxidase (HRP)-labeled streptavidin-biotin complex (Amersham) diluted 2,500 fold in the antibody dilution buffer and washed well with T-TBS. The reacting bands were detected by chemiluminescence using an ECL detection kit (Amersham) according to the manual. Consequently, as shown in Figure 15, a band that reacted with every antibody and is presumed to be derived from the 32-8-1 protein was detected in the liver tissue sample near the 130 kDa.

Example 7 Cloning of an upstream cDNA of 686-1-4 by RACE

The present inventors attempted to obtain a cDNA clone 5′ upstream of 686-1-4, which was cloned from the human heart, by the 5′ Rapid Amplification of cDNA Ends (RACE) method. The details follow.

(1) Cloning of cDNA clone D-2 by RACE

The present inventors performed 5′ Rapid Amplification of cDNA Ends (RACE) by using the Marathon Ready human brain cDNA (Clontech, #7400-1) as the adult human brain cDNA library. The 5′RACE mixture consisted of 5 µl of the Marathon Ready adult human brain cDNA, 1 µl each of 10 µM primer #878 (5′-TTTGTGCCCACCAGAGCCAAGTCAG-3′ (SEQ ID NO: 73)) and 10 µM AP1 primer (which came with the kit: 5′-CCATCCTAATACGACTCACTATAGGGC-3′ (SEQ ID NO: 42)), 1 µl of Advantage™ KlenTaq polymerase mix (Toyobo, CLK8417-1), and 33 µl of deionized water to make the total 50 µl. A PCR reaction using the Thermal Cycler (95°C for 1 minute, five cycles of 95°C for 5 seconds and 72°C for 4 minutes, five cycles of 95°C for 5 seconds and 70°C for 4 minutes, and 25 cycles of 95°C for 5 seconds and 68°C for 4 minutes) did not produce clearly detectable bands. Therefore, the reaction mixture was diluted 50 fold, and 5 µl of this was mixed with 5 µl of 10 x Advantage™ KlenTaq buffer (which came with the kit), 4 µl of 2.5 mM dNTP, 1 µl of 10 µM AP2 primer (which came with the kit; 5′ ACTCACTATAGGGCTCGAGCGGC-3 (SEQ ID NO: 44)), 1 µl of 10 µM 32-8-1 5′ RACE nested primer #757 (5′-GTGAAAGGGGTAAAGGCTTAGCAAC-3′ (SEQ ID NO: 74)), 1 µl of Advantage™ KlenTaq polymerase mix (Toyobo, CLK8417-1), and 33 µl of deionized water to make the total 50 µl. Nested PCR was performed at 95°C for 1 minute, five cycles of 95°C for 5 seconds and 72°C for four minutes, and five cycles of 95°C for 5 seconds and 70°C for 4 minutes. Subsequent treatment of 15 cycles at 95°C for 5 seconds and 68°C for 4 minutes produced a band of 1.8 kb. The products were separated on a 0.8% agarose gel. The corresponding band was excised and purified with the QIAquick gel extraction

kit (QIAGEN, 28706) and subjected to TA cloning according to the manual for the pGEM-T Vector System I (Promega, A3600). The resulting clone was designated D-2.

The nucleotide sequence determination was done as previously described, and the nucleotide sequence of 1,776 base pairs was determined by means of the cycle sequence method using the Dye Terminator Cycle Sequencing FS Ready Reaction kit (Perkin Elmer, Catalog #402122). The nucleotide sequence thus determined was found to encode 590 amino acids (SEQ ID NO: 75).

(2) Cloning of cDNA clone 1.2 kb#33 by RACE

The open reading frame that exists within the sequence of Clone D-2 is a sequence upstream of the 781st nucleotide of SEQ ID NO: 3. This open reading frame is not closed, that is, it does not have a stop codon, so it was assumed that the open reading frame continues further upstream. Thus the present inventors prepared a new primer and performed 5′ RACE. By using the Marathon Ready human brain cDNA (Clontech, #7400-1) as the template, the present inventors performed 5′ Rapid Amplification of cDNA Ends (RACE). The 5′RACE mixture consisted of 5 µl of the Marathon Ready adult human brain cDNA, 1 µl each of 10 µM primer B5R-1 (5′-GCAGATGGAGAACGGGAAACTATGG-3′ (SEQ ID NO: 76)) and 10 mM AP1 primer (which came with the kit; 5′-CCATCCTAATACGACTCACTATAGGGC-3′ (SEQ ID NO: 42)), 5 µl of 10 x Advantage™ KlenTaq buffer (which came with the kit), 4 µl of 2.5 mM dNTP, 1 µl of Advantage™ KlenTaq polymerase mix (Toyobo, CLK8417-1), and 33 µl of deionized water to make a total of 50 µl. A PCR reaction using the Thermal Cycler (95°C for 1 minute, five cycles of 95°C for 5 seconds and 72°C for 3 minutes, and five cycles of 95°C

for 5 seconds and 70°C for 3 minutes, followed by 25 cycles of 95°C for 5 seconds and 68°C for 3 minutes) did not produce detectable bands. Therefore, the reaction mixture was diluted 50 fold, and 5 µl of this was used as the template to perform nested PCR. The template was mixed with 5 µl of 10 x Advantage™ KlenTaq buffer (which came with the kit), 4 µl of 2.5 mM dNTP, 1 µl of 10 µM AP2 primer (which came with the kit; 5′-ACTCACTATAGGGCTCGAGCGGC-3 (SEQ ID NO: 44)), 1 µl of 10 µM primer B5R-2 (5′-GAACGGGAAACTATGGGGCTGACAA-3′ (SEQ ID NO: 77)), 1 µl of Advantage™ KlenTaq polymerase mix (Toyobo, CLK8417-1), and 33 µl of deionized water to make the total 50 µl. A reaction consisting of 95°C for 1 minute, five cycles of 95°C for 5 seconds and 72°C for 3 minutes, five cycles of 95°C for 5 seconds and 70°C for 3 minutes, followed by 15 cycles of 95°C for 5 seconds and 68°C for 3 minutes produced a band of 0.8 kb. The products were separated on a 0.8% agarose gel, the corresponding band was excised and purified with the QIAquick gel extraction kit (QIAGEN, 28706). It was then subjected to TA cloning according to the manual for the pGEM-T Vector System I (Promega, A3600). The resulting clone was designated 1.2 kb#33. The results of the nucleotide sequence determination (conducted as described before) revealed that the ATG codon starting with the 71st nucleotide corresponded to the first methionine, and that the clone encoded 235 amino acids. The last amino acid, arginine, corresponded to the arginine encoded by the nucleotides from position 108 to position 110 of clone D-2, and the nucleotides from position 1 to position 110 of the clone D-2 sequence overlapped with clone 1.2 kb#33. Therefore, the present inventors concluded that all the

upstream sequences of the deduced open reading frame were cloned.

(3) Analysis of the difference in amounts of expression in tissues

Amounts of mRNA expression in 24 types of tissues, including those that were examined by the northern blot above, were compared by RT-PCR. Human MTC panel I (K1402-1), human MTC panel II (K1421-1), and human fetal MTC panel I (K1425-1), which are commercially available from Clontech, were used as the cDNA. Results of the PCR reaction with the following reaction conditions are shown in Figure 16-A. PreMixTaq (10 µl; ExTaq TM Version) (Takara, PR003A), 2 µl of 2 µM 686D primer (SEQ ID NO: 66, corresponding to positions 2970 to 2989 of SEQ ID NO: 83, and to positions 1 to 20 of Figure 17), 2 µl of 2 µM 686E primer (SEQ ID NO: 67, corresponding to positions 3635 to 3654 of SEQ ID NO: 83, and to positions 666 to 685 of Figure 17), 1 µl of the first strand cDNA, and 5 µl of deionized water were mixed to make a total of 20 µl and reacted. Reaction of 94°C for 5 minutes, and 30 cycles of a three-step PCR reaction consisting of 94°C for 15 seconds, 50°C for 30 seconds, and 72°C for 30 seconds, followed by an extension reaction of 72°C for 7 minutes were performed.

As a result, high degrees of expression were seen in the brain (1), placenta (7), skeletal muscle (8), ovary (10), spleen (14), testis (15), fetal heart (18), fetal kidney (19), and fetal skeletal muscle (22). In addition, 15 µl of PreMixTaq (ExTaq TM Version) (Takara, PR003A), 3 µl of 2 µM 686D primer (SEQ ID NO: 66), 3 µl of 2 µM XE primer (SEQ ID NO: 15, which corresponds to

positions 3915 to 3934 of SEQ ID NO: 83, and to positions 946 to 965 of Figure 17), 1 µl of the first strand cDNA, and 8 µl of deionized water were mixed to make a total of 30 µl and reacted. Reaction of 94°C for 5 minutes, and 30 cycles of a three-step PCR reaction consisting of 94°C for 15 seconds, 50°C for 30 seconds, and 72°C for 1 minute, followed by an extension reaction of 72°C for 7 minutes were performed. As shown in Figure 16-B, bands of 750 bp, 850 bp, and 950 bp, which are presumed to be derived from three types of transcription products, were detected. Since the experiments in Figure 16-A and 16-B both used the same 686D primer, three types of splicing should take place within the sequences that exist in between the 686E primer and the XE primer, producing the transcription products of different lengths. The three types of PCR products were cloned from those of the fetal heart that showed the highest expression. Cloning was done by excising the corresponding bands and purifying them using the QIAquick gel extraction kit (QIAGEN, 28706), and by following the manual for the pGEM-T Vector System I (Promega, A3600).

(4) Analysis of the gene sequences of clones FH750, FH850, and FH950

The nucleotide sequences for the cloned PCR products were determined according to the method described above. The determined nucleotide sequences of FH750, FH850, and FH950 are shown in SEQ ID NO: 79, 80, and 81, respectively. The sequences of the three kinds of DNA are aligned and shown in Figures 17 and 18. Although the sequences of the three kinds of DNA are identical up to sequence position 731, FH850 diverges from FH950 beginning with the 819th nucleotide, which suggests that splicing takes place at

some sequence immediately preceding this position. As a result of this splicing, FH850 generates a stop codon with the sequence from position 819 to position 821, and the translation is expected to terminate at this position.

In FH750, positions 732 to 941 of the FH950 sequence are spliced out, creating a 210 bp deletion of the gene. However, the protein encoded by the transcription product of the FH750 type splicing is predicted to lack 70 amino acids compared with FH950 type splicing since the sequences before and after the deleted region are expected to be translated in the same frame as in those of FH950.

The sequence obtained by combining 1.2 kb#33 (SEQ ID NO: 78), D-2 (SEQ ID NO: 75), and SEQ ID NO: 3 (Figure 26) was bordered by primer 686D and primer XE derived from the 686-1-4 sequence and was identical to FH750. The clone corresponding to the transcription product expected to be generated by the FH750 type splicing was designated 32-8-1a. (The amino acid sequence of the protein is shown in SEQ ID NO: 82, and the nucleotide sequence of the cDNA is shown in SEQ ID NO: 85.) Clone 32-8-1a can code for 2,000 amino acids. The clone corresponding to the transcription product expected to be generated by the FH950 type splicing was designated 32-8-1b. (The amino acid sequence of the protein is shown in SEQ ID NO: 83, and the nucleotide sequence of the cDNA is shown in SEQ ID NO: 86.) Code 32-8-1b can code for 2,070 amino acids. These two genes possess 13 PDZ domains. Furthermore, the transcription product generated by the FH850 type splicing will contain a stop codon in this region, and it can only code for 1,239 amino acids. This means that it possesses only seven PDZ domains. The clone corresponding to this transcription product was designated 32-8-1c. (The amino acid sequence

of the protein is shown in SEQ ID NO: 84, and the nucleotide sequence of the cDNA is shown in SEQ ID NO: 87.)

Sequence comparisons between "32-8-1b" and "AF00168" (Mus musculus 90RF binding protein 1 (9BP-1) mRNA, partial cds.) are shown in Figure 20; between "32-8-1b" and "AJ001319" (Homo sapiens mRNA for multi PDZ domain protein), in Figure 21; and between "32-8-1b" and "AJ001320" (Rattus norvegius mRNA for multi PDZ domain protein), in Figures 22 through 24. The PDZ domain sequences of the protein encoded by the 32-8-1b gene (SEQ ID NO: 83) are also shown in Figure 25.

(6) Identification of the 32-8-1b high molecular weight protein by western blotting

Human neuroblastoma SH-SY5Y cells and human teratocarcinoma NT-2 cells stimulated by retinoic acid to differentiate into neurons were directly dissolved into SDS-PAGE sample buffer and separated on a 7.5% SDS-polyacrylamide gel by electrophoresis. The proteins were transferred onto Immobilon-P (Millipore) using the Semidry blotter (Bio-Rad) according to the methods described in the manual. The filter was then blocked at 4°C overnight with 5% skim milk (DIFCO), 2.5% bovine serum albumin (Sigma, A5940), and T-TBS (20 mM Tris-HCl (pH 7.5), 150 mM NaCl, and 0.05% Tween 20). It was next reacted at room temperature for 1 hour with the individual rabbit antisera diluted 5,000 fold in the antibody dilution buffer (1% skim milk, 0.5% bovine serum albumin, and T-TBS). It was then reacted at room temperature for 1 hour with the biotin-labeled anti-rabbit Ig diluted 1,000 fold in the antibody dilution buffer. Finally, it was reacted at room temperature for 15 minutes with the horseradish peroxidase

(HRP)-labeled streptavidin-biotin complex (Amersham) diluted 2,500 fold in the antibody dilution buffer and washed well with T-TBS. The reacting bands were then detected by chemiluminescence using an ECL detection kit (Amersham) according to the manual. As shown in Figure 19, a protein whose molecular weight exceeds 250 kDa was detected in both SH-SY5Y and NT-N with either rabbit antisera #1 raised against peptide 32-8-1-17 or rabbit antisera #3D raised against PDZ56 that had been expressed as a GST fusion protein and digested with thrombin to retain only the 32-8-1 gene product. The assumption that the full-length 32-8-1b protein consists of 2,070 amino acids agrees with the molecular weight observed.

Industrial Applicability

By utilizing the proteins and the gene of the present invention, it has become possible to isolate the proteins and their genes that bind to the PDZ domains of the proteins of the present invention. It has been reported that proteins having the PDZ domain interact with the proteins that bind to them and function in the signal transduction related to cell proliferation, cell cycle, malignant conversion, apoptosis, cell adhesion, etc. Therefore, if the relationships between the proteins of the present invention and the proteins that interact with them, as well as the related signal transduction pathways, can be clarified, it should be possible to treat and diagnose disorders related to cell proliferation and others described above by targeting these proteins or their genes. These proteins and their genes are therefore useful for developing therapeutic medicines and diagnostic medicines.

What is claimed is:

1. A substantially pure polypeptide comprising an amino acid sequence at least 85% identical to any one of SEQ ID NOs:1, 2, 82, 83, or 84, wherein the polypeptide contains a PDZ domain sequence.

2. The polypeptide of claim 1, wherein the amino acid sequence is at least 90% identical to any one of SEQ ID NOs: 1, 2, 82, 83, or 84.

3. A substantially pure polypeptide comprising the sequence of any one of SEQ ID NOs: 1, 2, 82, 83, or 84.

4. A substantially pure polypeptide comprising the amino acid sequence of any one of SEQ ID NOs: 1, 2, 82, 83, or 84, with up to 50 conservative amino acid substitutions, wherein the polypeptide contains a PDZ domain sequence.

5. A substantially pure polypeptide encoded by a nucleic acid that hybridizes under high stringency conditions to a probe the sequence of which consists of any one of SEQ ID NOs:3, 59, 75, 78, 79, 80, 81, 85, 86, or 87, wherein the polypeptide contains a PDZ domain sequence.

6. An isolated nucleic acid encoding the polypeptide of claim 1.

7. An isolated nucleic acid encoding the polypeptide of claim 3.

8. An isolated nucleic acid encoding the polypeptide of claim 4.

9. An isolated nucleic acid comprising a strand that hybridizes under stringent conditions to a single stranded probe, the sequence of which consists of any one of SEQ ID NOs: 3, 59, 75, 78, 79, 80, 81, 85, 86, or 87, or the complement of any one of SEQ ID NOs: 3, 59, 75, 78, 79, 80, 81, 85, 86, or 87.

10. The isolated nucleic acid of claim 9, wherein the nucleic acid encodes a polypeptide that contains a PDZ domain.

11. The nucleic acid of claim 10, wherein the amino acid sequence of the polypeptide comprises any one of SEQ ID NOs:1, 2, 82, 83, or 84.

12. The nucleic acid of claim 9, wherein the strand is at least 15 nucleotides in length.

13. The nucleic acid of claim 12, wherein the nucleic acid is an antisense nucleic acid that inhibits expression of a polypeptide comprising any one of SEQ ID NOs:1, 2, 82, 83, or 84.

14. A vector comprising the nucleic acid of claim 6.

15. A vector comprising the nucleic acid of claim 7.

16. A vector comprising the nucleic acid of claim 8.

17. A vector comprising the nucleic acid of claim 9.

18. A vector comprising the nucleic acid of claim 10.

19. A cultured host cell comprising the nucleic acid of claim 6.

20. A cultured host cell comprising the nucleic acid of claim 7.

21. A cultured host cell comprising the nucleic acid of claim 8.

22. A cultured host cell comprising the nucleic acid of claim 9.

23. A cultured host cell comprising the nucleic acid of claim 10.

24. An antibody that specifically binds to the polypeptide of claim 1.

25. A method of producing a polypeptide, the method comprising isolating the polypeptide from the cultured host cell of claim 19.

26. A method of screening for a compound that specifically binds to a polypeptide, the method comprising contacting a test compound with the polypeptide of claim 1, and comparing the extent to which the test compound binds to the polypeptide with the extent to which a reference compound binds to the polypeptide, wherein a test compound binding to the polypeptide to a greater extent than the reference compound indicates that the test compound specifically binds to the polypeptide.

27. The method of claim 26, wherein the test compound is a test polypeptide.

28. The method of claim 27, further comprising identifying the gene that encodes the test polypeptide.

29. A compound that binds to the polypeptide of claim 1.

30. The compound of claim 29, wherein the compound is a polypeptide.

31. A gene encoding the compound of claim 30.

32. The nucleic acid of claim 12, wherein the nucleic acid is an antisense nucleic acid that inhibits expression of a polypeptide comprising any one of SEQ ID NOs:1, 2, 82, 83, or 84.

33. A fusion protein comprising any one of SEQ ID NOs:1, 2, 82, 83, or 84 and another amino acid sequence.

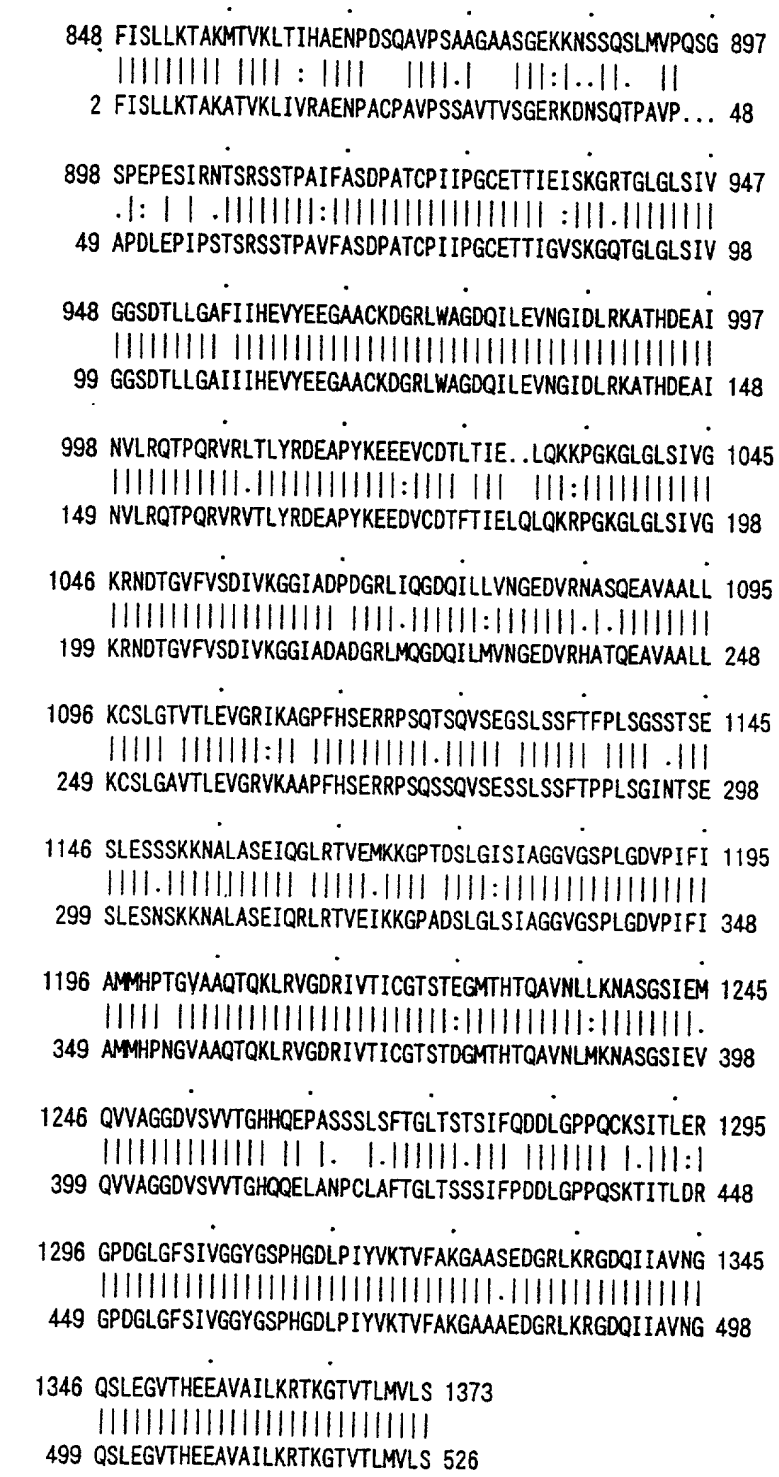
34. The fusion protein of claim 33, wherein the other amino acid sequence is specifically bound by an antibody.

PROTEIN HAVING PDZ DOMAIN SEQUENCE

Abstract of the Disclosure

While analyzing changes in gene expression by TNFα in human umbilical vascular endothelial cells, a gene showing enhanced expression due to stimulation with TNFα was isolated. After screening with this gene as a probe, a gene encoding a protein was isolated. Analysis of the protein encoded by this isolated gene revealed that this novel protein has never been reported and has a PDZ domain in its molecule that plays an important role in protein-protein interactions.

Figure 1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2 FISLLKTAKATVKLIVRAENPACPAVPSSAVTVSGERKDNSQTPAVP... 48
898 SPEPESIRNTSRSSTPAIFASDPATCPIIPGCETTIEISKGRTGLGLSIV 947
49 APDLEPIPSTSRSSTPAVFASDPATCPIIPGCETTIGVSKGQTGLGLSIV 98
948 GGSDTLLGAFIIHEVYEEGAACKDGRLWAGDQILEVNGIDLRKATHDEAI 997
99 GGSDTLLGAIIIHEVYEEGAACKDGRLWAGDQILEVNGIDLRKATHDEAI 148
998 NVLRQTPQRVRLTLYRDEAPYKEEEVCDTLTIE..LQKKPGKGLGLSIVG 1045
149 NVLRQTPQRVRVTLYRDEAPYKEEDVCDTFTIELQLQKRPGKGLGLSIVG 198
1046 KRNDTGVFVSDIVKGGIADPDGRLIQGDQILLVNGEDVRNASQEAVAALL 1095
199 KRNDTGVFVSDIVKGGIADADGRLMQGDQILMVNGEDVRHATQEAVAALL 248
1096 KCSLGTVTLEVGRIKAGPFHSERRPSQTSQVSEGSLSSFTFPLSGSSTSE 1145
249 KCSLGAVTLEVGRVKAAPFHSERRPSQSSQVSESSLSSFTPPLSGINTSE 298
1146 SLESSSKKNALASEIQGLRTVEMKKGPTDSLGISIAGGVGSPLGDVPIFI 1195
299 SLESNSKKNALASEIQRLRTVEIKKGPADSLGLSIAGGVGSPLGDVPIFI 348
1196 AMMHPTGVAAQTQKLRVGDRIVTICGTSTEGMTHTQAVNLLKNASGSIEM 1245
349 AMMHPNGVAAQTQKLRVGDRIVTICGTSTDGMTHTQAVNLMKNASGSIEV 398
1246 QVVAGGDVSVVTGHHQEPASSSLSFTGLTSTSIFQDDLGPPQCKSITLER 1295
399 QVVAGGDVSVVTGHQQELANPCLAFTGLTSSSIFPDDLGPPQSKTITLDR 448
1296 GPDGLGFSIVGGYGSPHGDLPIYVKTVFAKGAASEDGRLKRGDQIIAVNG 1345
449 GPDGLGFSIVGGYGSPHGDLPIYVKTVFAKGAAAEDGRLKRGDQIIAVNG 498
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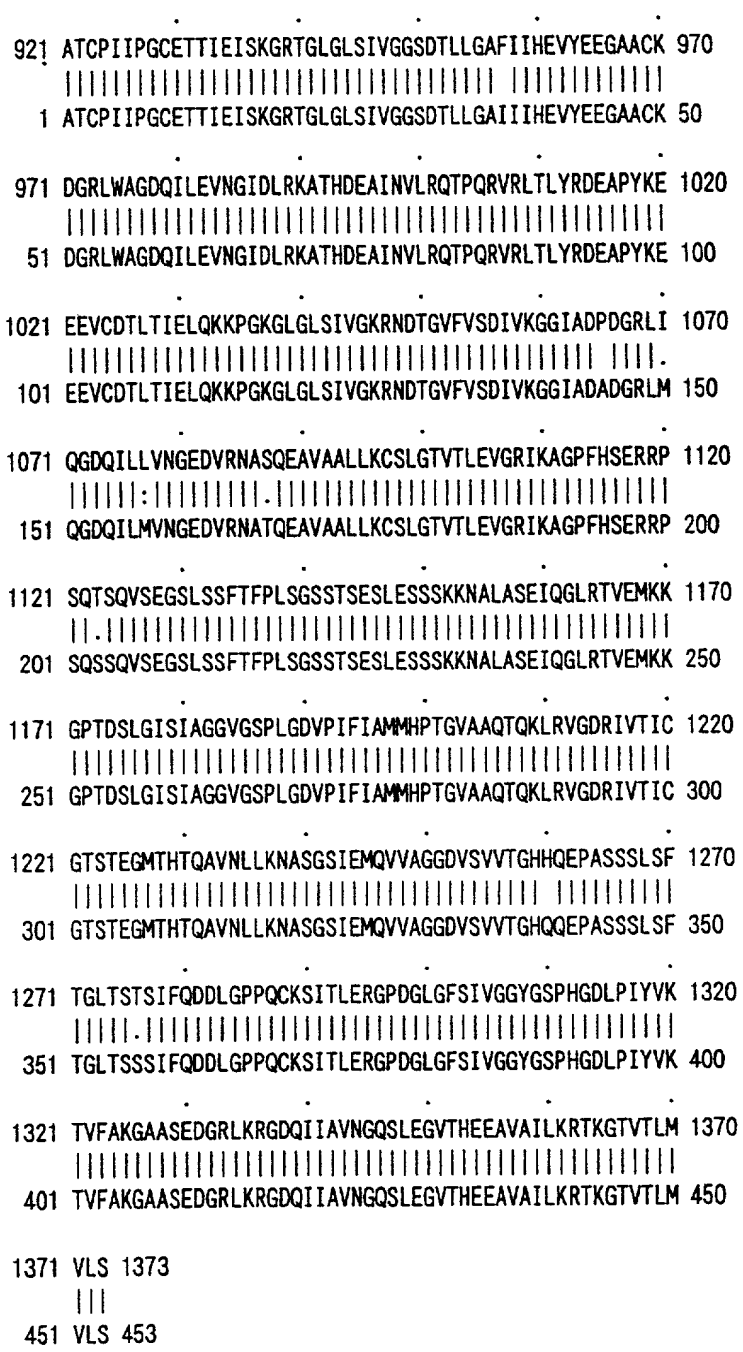
Figure 2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1021 EEVCDTLTIELQKKPGKGLGLSIVGKRNDTGVFVSDIVKGGIADPDGRLI 1070
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151 QGDQILMVNGEDVRNATQEAVAALLKCSLGTVTLEVGRIKAGPFHSERRP 200
1121 SQTSQVSEGSLSSFTFPLSGSSTSESLESSSKKNALASEIQGLRTVEMKK 1170
201 SQSSQVSEGSLSSFTFPLSGSSTSESLESSSKKNALASEIQGLRTVEMKK 250
1171 GPTDSLGISIAGGVGSPLGDVPIFIAMMHPTGVAAQTQKLRVGDRIVTIC 1220
251 GPTDSLGISIAGGVGSPLGDVPIFIAMMHPTGVAAQTQKLRVGDRIVTIC 300
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301 GTSTEGMTHTQAVNLLKNASGSIEMQVVAGGDVSVVTGHQQEPASSSLSF 350
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1321 TVFAKGAASEDGRLKRGDQIIAVNGQSLEGVTHEEAVAILKRTKGTVTLM 1370
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1371 VLS 1373
451 VLS 453


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670 SDVDQNAEEIQTPLAMWEAGIQAIELEKGSRGLGFSILDYQDPIDPANTV 719
101 IIIRSLVPGGIAEKDGRLLPGDRLMFVNDVNLENSSLEEAVEALKGAPSG 150
720 IVIRSLVPGGIAEKDGRLFPGDRLMFVNDINLENSTLEEAVEALKGAPSG 769
151 TVRIGVAKPLPLSPEEGYVSAKEDSFLYPPHSCEEAGLADKPLFRADLAL 200
770 MVRIGVAKPLPLSPEEGYVSAKEDTFLCSPHTCKEMGLSDKALFRADLAL 819
201 VGTNDADLVDESTFESPYSPENDSIYSTQASILSLHGSSCGDGLNYGSSL 250
820 IDTPDAESVAESRFESQFSPDNDSVYSTQASVLSLHDGACSDGMNYGPSL 869
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919 GFTVSDYTPANAVEQKYECANTVAWTPSQLPSG.LSTTELAPALPAVAPK 967
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1015 GLGVIVRSIIHGGAISRDGRIAVGDCILSINEESTISLTNAQARAMLRRH 1064
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1315 DEFGYSWKNIQERYGTLTGQLHMIELEKGHSGLGLSLAGNKDRTRMSVFI 1364
681 VGIDPNGAAGKDGRLQIADELLEINGQILYGRSHQNASSIIKCAPSKVKI 730
1365 VGIDPTGAAGRDGRLQIADELLEINGQILYGRSHQNASSIIKCAPSKVKI 1414
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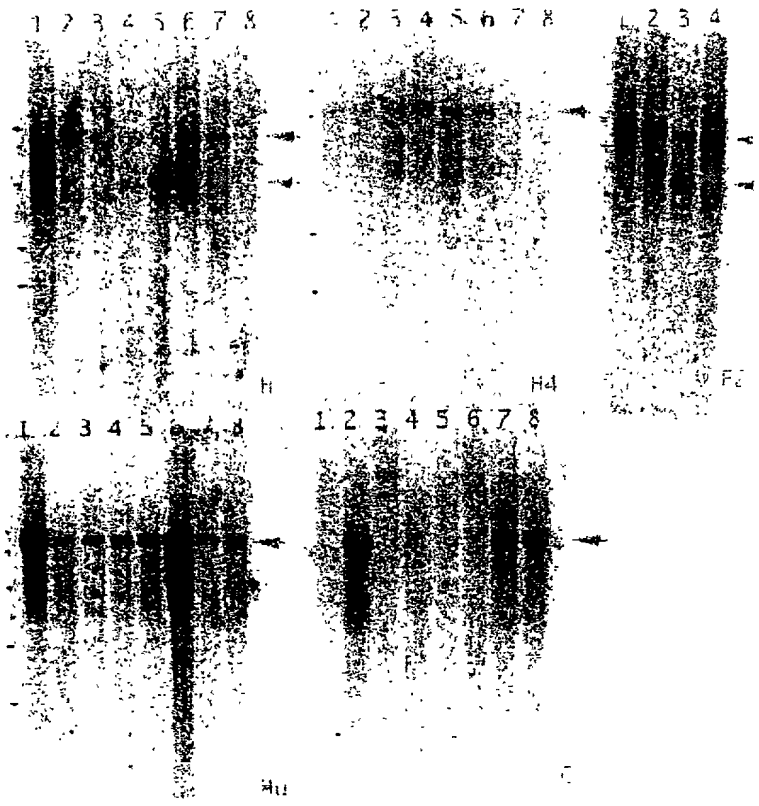
Figure 3


781 FKNVQHLELPKDQGGLGIAISEEDTLSGVIIKSLTEHGVAATDGRLKVGD 830
1465 LTNVYHLELPKDQGGLGIAICEEDTLNGVTIKSLTERGGAAKDGRLKPGD 1514
831 QILAVDDEIVVGYPIEKFISLLKTAKMTVKLTIHAENPDSQAVPSAAGAA 880
1515 RILAVDDELVAGCPIEKFISLLKTAKTTVKLTVGAENPGCQAVPSAAVTA 1564
881 SGEKKNSSQSLMVPQSGSPEPESIRNTSRSSTPAIFASDPATCPIIPGCE 930
1565 SGERKDSSQTPAVP...APDLEPIPSTSRSSTPAIFASDPATCPIIPGCE 1611
931 TTIEISKGRTGLGLSIVGGSDTLLGAFIIHEVYEEGAACKDGRLWAGDQI 980
1612 TTIEISKGQTGLGLSIVGGSDTLLGAIIIHEVYEEGAACKDGRLWAGDQI 1661
981 LEVNGIDLRKATHDEAINVLRQTPQRVRLTLYRDEAPYKEEEVCDTLTIE 1030
1662 LEVNGIDLRKATHDEAINVLRQTPQRVRLTLYRDEAPYKEEDVCDTFTVE 1711
1031 LQKKPGKGLGLSIVGKRNDTGVFVSDIVKGGIADPDGRLIQGDQILLVNG 1080
1712 LQKRPGKGLGLSIVGKRNDTGVFVSDIVKGGIADADGRLMQGDQILMVNG 1761
1081 EDVRNASQEAVAALLKCSLGTVTLEVGRIKAGPFHSERRPSQTSQVSEGS 1130
1762 EDVRNATQEAVAALLKCSLGTVTLEVGRIKAAPFHSERRPSQSSQVSESS 1811
1131 LSSFTFPLSGSSTSESLESSSKKNALASEIQGLRTVEMKKGPTDSLGISI 1180
1812 LSSFSLPRSGIHTSESSESSAKKNALASEIQGLRTVEIKKGPADALGLSI 1861
1181 AGGVGSPLGDVPIFIAMMHPTGVAAQTQKLRVGDRIVTICGTSTEGMTHT 1230
1862 AGGVGSPLGDVPIFIAMMHPNGVAAQTQKLRVGDRIVTICGTSTDGMTHT 1911
1231 QAVNLLKNASGSIEMQVVAGGDVSVVTGHHQEPASSSLSFTGLTSTSIFQ 1280
1912 QAVNLMKNASGSIEVQVVAGGDVSVVTGHQQELANPCLAFTGLTSSTIFP 1961
1281 DDLGPPQCKSITLERGPDGLGFSIVGGYGSPHGDLPIYVKTVFAKGAASE 1330
1962 DDLGPPQSKTITLDRGPDGLGFSIVGGYGSPHGDLPIYVKTVFAKGAAAE 2011
1331 DGRLKRGDQIIAVNGQSLEGVTHEEAVAILKRTKGTVTLMVLS 1373
2012 DGRLKRGDQIIAVNGQSLEGVTHEEAVAILKRTKGTVTLMVLS 2054

Figure 4

Figure 5



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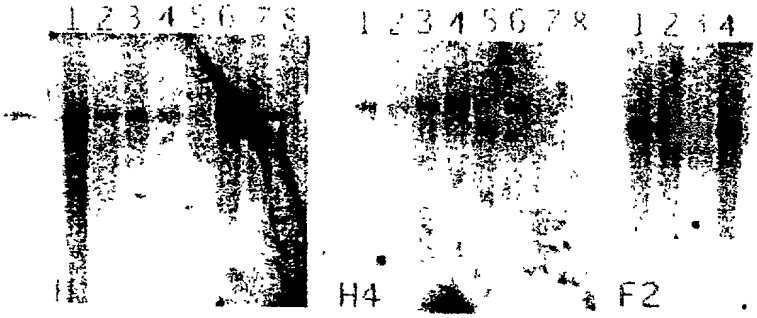

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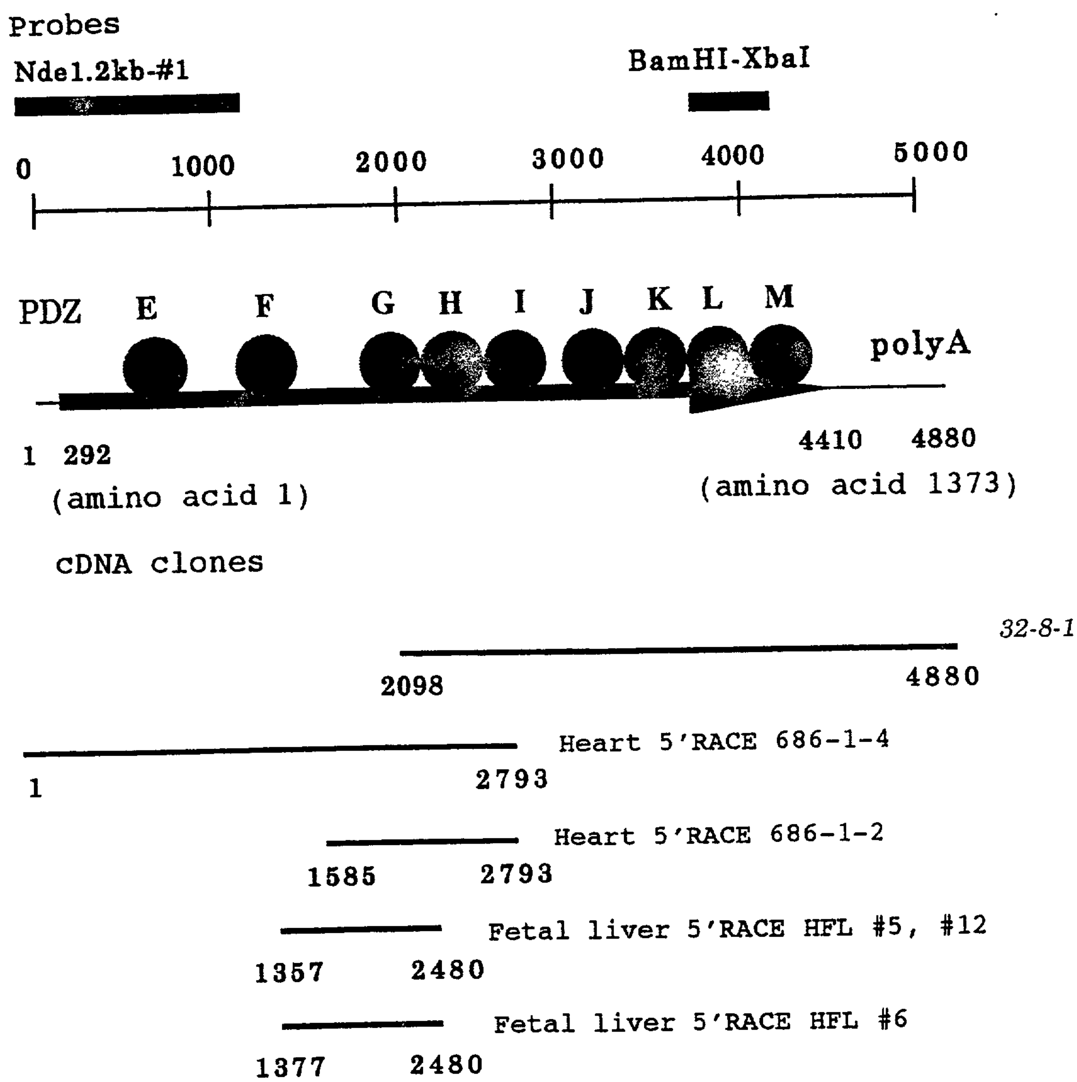
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Nde1.2kb-#1
BamHI-XbaI
0
1000
2000
3000
4000
5000
PDZ
E
F
G
H
I
J
K
L
M
polyA
1
292
(amino acid 1)
4410
4880
(amino acid 1373)
cDNA clones
32-8-1
2098
4880
Heart 5'RACE 686-1-4
1
2793
Heart 5'RACE 686-1-2
1585
2793
Fetal liver 5'RACE HFL #5, #12
1357
2480
Fetal liver 5'RACE HFL #6
1377
2480

Figure 8

	1				50
PDZ-E	AGIQHIELE.	KGSKGLGFSI	LDYQD.....	PIDPASTVII	IRSLVPGGIA
PDZ-F	QNVSKESFER	TINIAKGNSS	LGMTV.....	SANKDGLGMI	VRSIIHGGAI
PDZ-G	NQPRRVELWR	EPSKSLGISI	VGGRGMGSRL	SNGEVMRGIF	IKHVLEDSPA
PDZ-H	GELHMIELEK	GHS.GLGLSL	AGNKD.....	RSR.M..SVF	IVGIDPNGAA
PDZ-I	KNVQHLELPK	DQG.GLGIAI	....	SEEDTLSGVI	IKSLTEHGVA
PDZ-J	GCETTIEISK	GRT.GLGLSI	VGGSD.....	TLL.G..AFI	IHEVYEEGAA
PDZ-K	CDTLTIELQK	KPGKGLGLSI	VGKRN.....	.....DTGVF	VSDIVKGGIA
PDZ-L	QGLRTVEMKK	GPTDSLGISI	AGGVG.....	SPL.GDVPIF	IAMMHPTGVA
PDZ-M	PQCKSITLER	GP.DGLGFSI	VGGYG.....	SPH.GDLPIY	VKTVFAKGAA

	51				96
PDZ-E	EKDGRLLPGD	RLMFVNDVNL	ENSSLEEAVE	ALKGAPSGTV	RIGVAK
PDZ-F	SRDGRIAIGD	CILSINEEST	ISVTNAQARA	MLRRHSLIGP	DIKITY
PDZ-G	GKNGTLKPGD	RIVEAPSQSE	SEPEKAPLCS	VPPPPPSAFA	EMGSDH
PDZ-H	GKDGRLQIAD	ELLEINGQIL	YGRSHQNASS	IIKCAP.SKV	KIIFIR
PDZ-I	ATDGRLKVGD	QILAVDDEIV	VGYPIEKFIS	LLKTAKM.TV	KLTIHA
PDZ-J	CKDGRLWAGD	QILEVNGIDL	RKATHDEAIN	VLRQTP.QRV	RLTLYR
PDZ-K	DPDGRLIQGD	QILLVNGEDV	RNAS.QEAVA	ALLKCSLGTV	TLEVGR
PDZ-L	AQTQKLRVGD	RIVTICGTST	EGMTHTQAVN	LLKNAS.GSI	EMQVVA
PDZ-M	SEDGRLKRGD	QIIAVNGQSL	EGVTHEEAVA	ILKRTK.GTV	TLMVLS

Figure 9

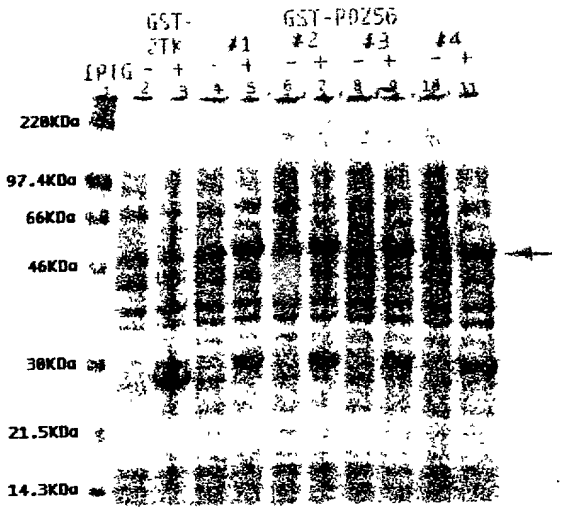

GST-
GST-P0256
#1
#2
#3
#4
IPTG - + - + - + - + - +
1 2 3 4 5 6 7 8 9 10 11
220KDa
97.4KDa
66KDa
46KDa
30KDa
21.5KDa
14.3KDa

Figure 10

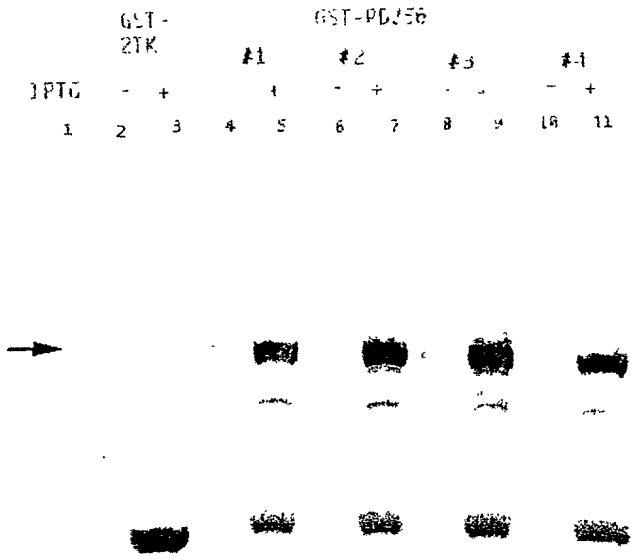


Figure 11

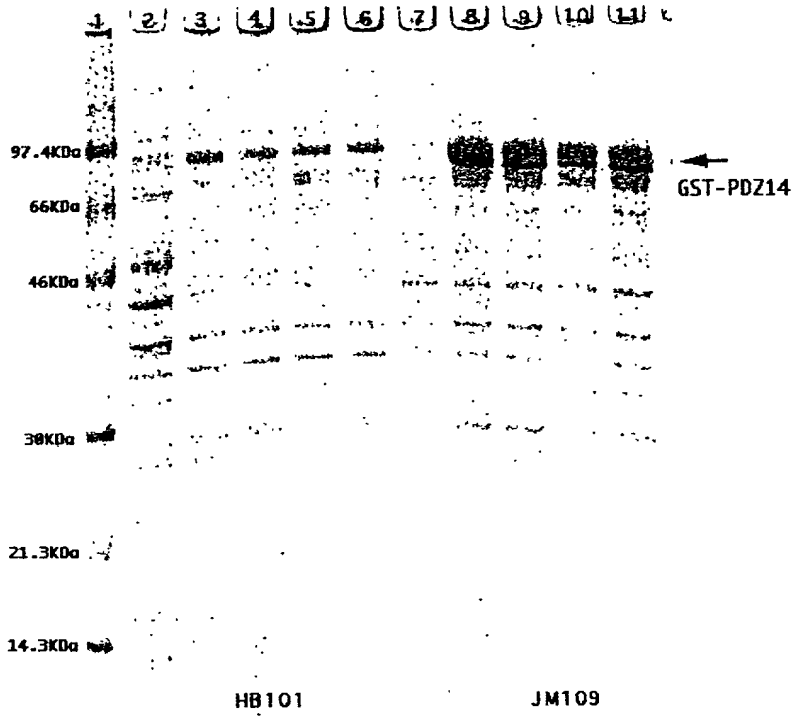
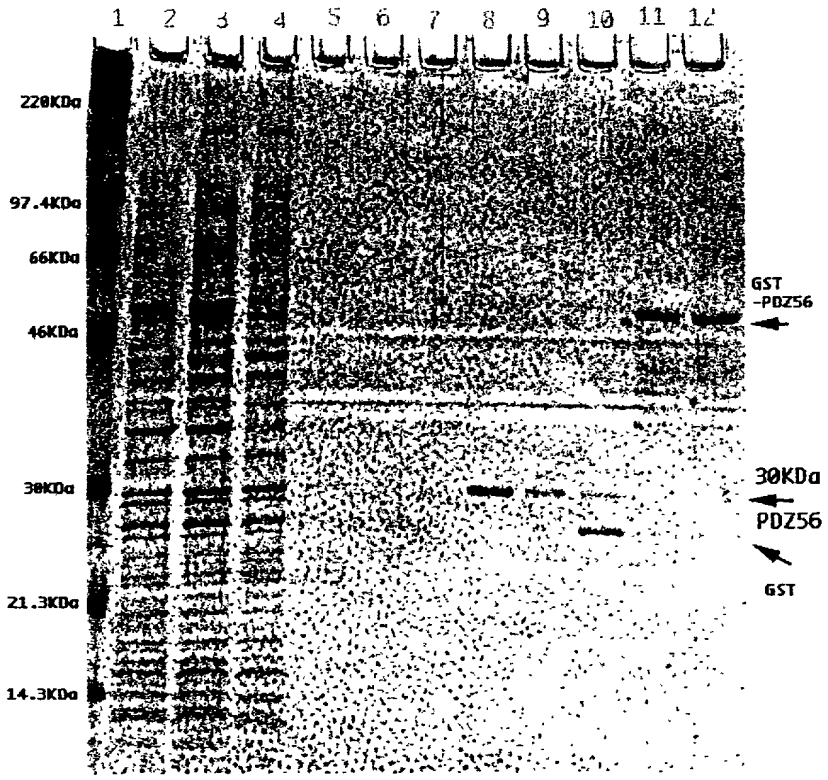

1
2
3
4
5
6
7
8
9
10
11
97.4KDa
66KDa
46KDa
30KDa
21.3KDa
14.3KDa
GST-PDZ14
HB101
JM109

Figure 12


1
2
3
4
5
6
7
8
9
10
11
12
220KDa
97.4KDa
66KDa
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30KDa
21.3KDa
14.3KDa
GST
-PDZ56
30KDa
PDZ56
GST

Figure 13

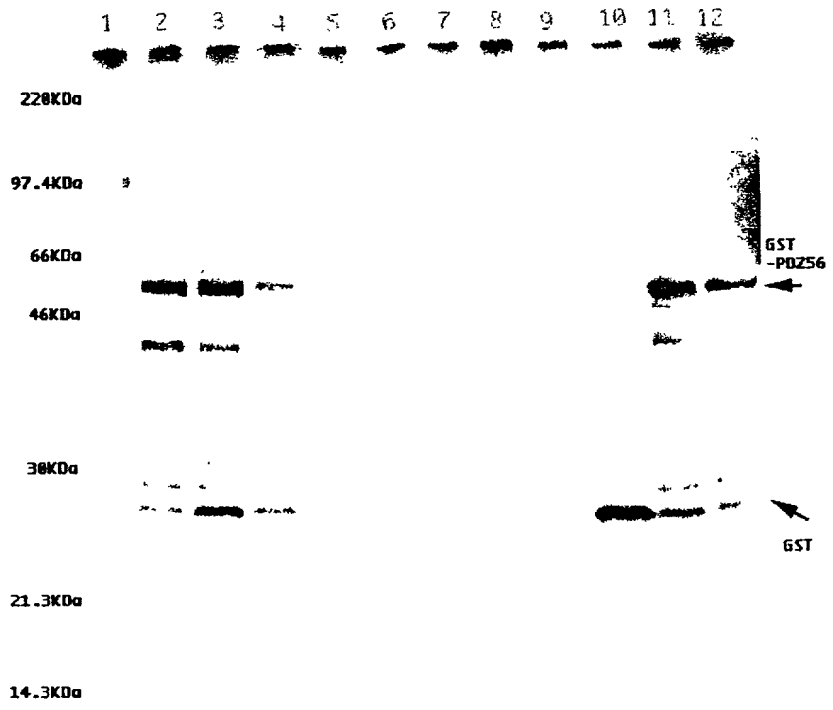
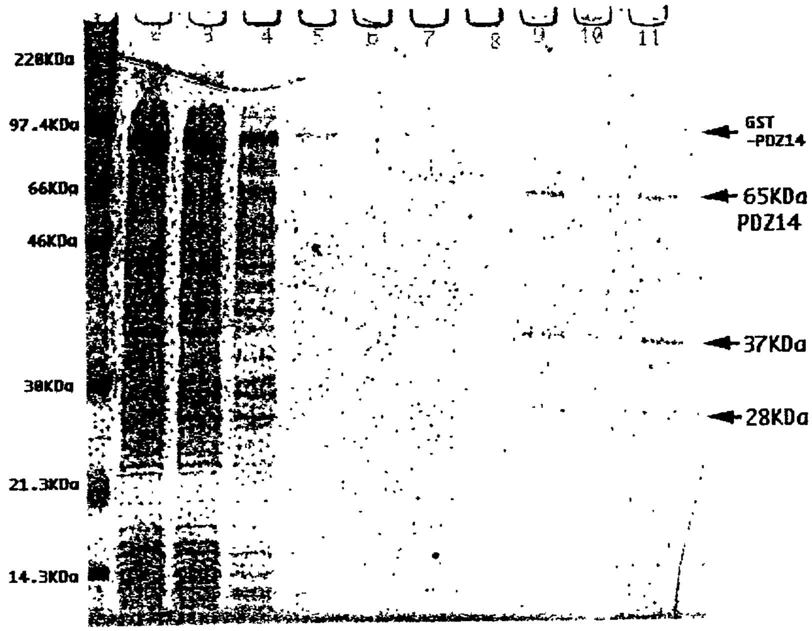

1
2
3
4
5
6
7
8
9
10
11
12
220KDa
97.4KDa
66KDa
46KDa
30KDa
21.3KDa
14.3KDa
GST
-PDZ56
GST

Figure 14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66KDa
46KDa
30KDa
21.3KDa
14.3KDa
2
3
4
5
6
7
8
9
10
11
GST
-PDZ14
65KDa
PDZ14
37KDa
28KDa

Figure 15


T Sk Lv H B
T Sk Lv H B
T Sk Lv H B
anti-32-8-1-17
anti-PDZ14
anti-PDZ56
KDa
220
97.4
66
46
30
21.5
14.3

Figure 16

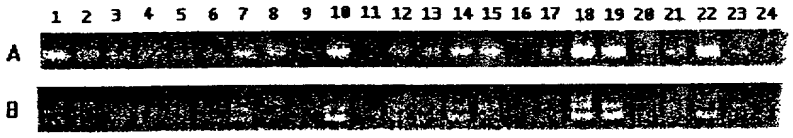

Figure 17

```
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FH750 TTCCTTCTGT GCTACCCGAT TCAGCTGGAA AGGGCTCTGA GTACCTGCTT
FH850 TTCCTTCTGT GCTACCCGAT TCAGCTGGAA AGGGCTCTGA GTACCTGCTT
FH950 TTCCTTCTGT GCTACCCGAT TCAGCTGGAA AGGGCTCTGA GTACCTGCTT

      51                                               100
FH750 GAACAGAGCT CCCTGGCCTG TAATGCTGAG TGTGTCATGC TTCAAAATGT
FH850 GAACAGAGCT CCCTGGCCTG TAATGCTGAG TGTGTCATGC TTCAAAATGT
FH950 GAACAGAGCT CCCTGGCCTG TAATGCTGAG TGTGTCATGC TTCAAAATGT

      101                                              150
FH750 ATCTAAAGAA TCTTTTGAAA GGACTATTAA TATAGCAAAA GGCAATTCTA
FH850 ATCTAAAGAA TCTTTTGAAA GGACTATTAA TATAGCAAAA GGCAATTCTA
FH950 ATCTAAAGAA TCTTTTGAAA GGACTATTAA TATAGCAAAA GGCAATTCTA

      151                                              200
FH750 GCCTAGGAAT GACAGTTAGT GCTAATAAAG ATGGCTTGGG GATGATCGTT
FH850 GCCTAGGAAT GACAGTTAGT GCTAATAAAG ATGGCTTGGG GATGATCGTT
FH950 GCCTAGGAAT GACAGTTAGT GCTAATAAAG ATGGCTTGGG GATGATCGTT

      201                                              250
FH750 CGAAGCATTA TTCATGGAGG TGCCATTAGT CGAGATGGCC GGATTGCCAT
FH850 CGAAGCATTA TTCATGGAGG TGCCATTAGT CGAGATGGCC GGATTGCCAT
FH950 CGAAGCATTA TTCATGGAGG TGCCATTAGT CGAGATGGCC GGATTGCCAT

      251                                              300
FH750 TGGGGACTGC ATCTTGTCCA TTAATGAAGA GTCTACCATC AGTGTAACCA
FH850 TGGGGACTGC ATCTTGTCCA TTAATGAAGA GTCTACCATC AGTGTAACCA
FH950 TGGGGACTGC ATCTTGTCCA TTAATGAAGA GTCTACCATC AGTGTAACCA

      301                                              350
FH750 ATGCCCAGGC ACGAGCTATG TTGAGAAGAC ATTCTCTCAT TGGCCCTGAC
FH850 ATGCCCAGGC ACGAGCTATG TTGAGAAGAC ATTCTCTCAT TGGCCCTGAC
FH950 ATGCCCAGGC ACGAGCTATG TTGAGAAGAC ATTCTCTCAT TGGCCCTGAC

      351                                              400
FH750 ATAAAAATTA CTTATGTGCC TGCAGAACAT TTGGAAGAGT TCAAAATAAG
FH850 ATAAAAATTA CTTATGTGCC TGCAGAACAT TTGGAAGAGT TCAAAATAAG
FH950 ATAAAAATTA CTTATGTGCC TGCAGAACAT TTGGAAGAGT TCAAAATAAG

      401                                              450
FH750 CTTGGGACAA CAATCTGGAA GAGTAATGGC ACTGGATATT TTTTCTTCAT
FH850 CTTGGGACAA CAATCTGGAA GAGTAATGGC ACTGGATATT TTTTCTTCAT
FH950 CTTGGGACAA CAATCTGGAA GAGTAATGGC ACTGGATATT TTTTCTTCAT

      451                                              500
FH750 ACACTGGCAG AGACATTCCA GAATTACCAG AGCGAGAAGA GGGAGAGGGT
FH850 ACACTGGCAG AGACATTCCA GAATTACCAG AGCGAGAAGA GGGAGAGGGT
FH950 ACACTGGCAG AGACATTCCA GAATTACCAG AGCGAGAAGA GGGAGAGGGT

      501                                              550
FH750 GAAGAAAGCG AACTTCAAAA CACAGCATAT AGCAATTGGA ATCAGCCCAG
FH850 GAAGAAAGCG AACTTCAAAA CACAGCATAT AGCAATTGGA ATCAGCCCAG
FH950 GAAGAAAGCG AACTTCAAAA CACAGCATAT AGCAATTGGA ATCAGCCCAG

      551                                              600
FH750 GCGGGTGGAA CTCTGGAGAG AACCAAGCAA ATCCTTAGGC ATCAGCATTG
FH850 GCGGGTGGAA CTCTGGAGAG AACCAAGCAA ATCCTTAGGC ATCAGCATTG
FH950 GCGGGTGGAA CTCTGGAGAG AACCAAGCAA ATCCTTAGGC ATCAGCATTG

      601                                              650
FH750 TTGGTGGACG AGGGATGGGG AGTCGGCTAA GCAATGGAGA AGTGATGAGG
FH850 TTGGTGGACG AGGGATGGGG AGTCGGCTAA GCAATGGAGA AGTGATGAGG
FH950 TTGGTGGACG AGGGATGGGG AGTCGGCTAA GCAATGGAGA AGTGATGAGG

      651                                              700
FH750 GGCATTTTCA TCAAACATGT TCTGGAAGAT AGTCCAGCTG GCAAAAATGG
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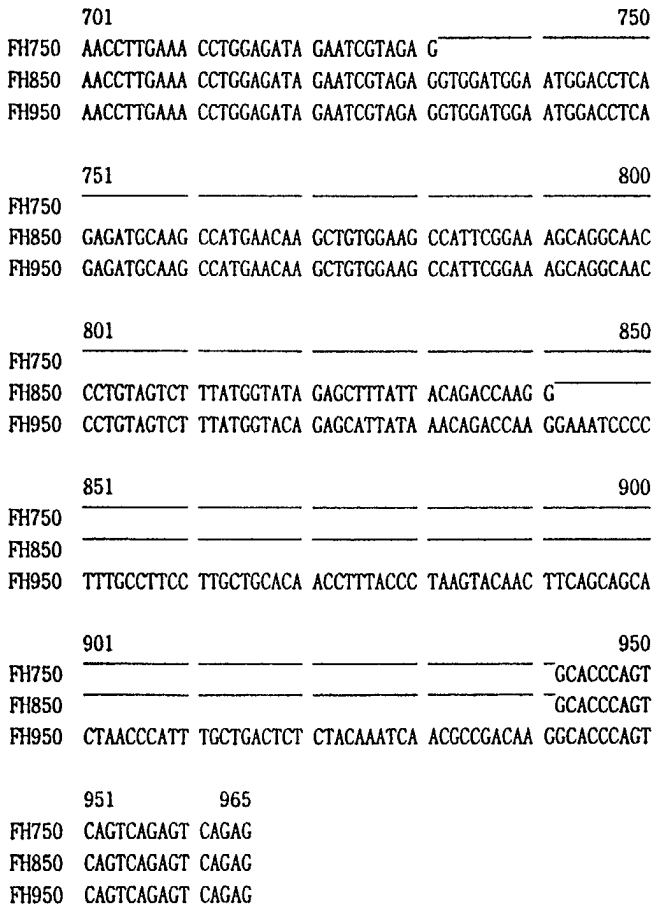
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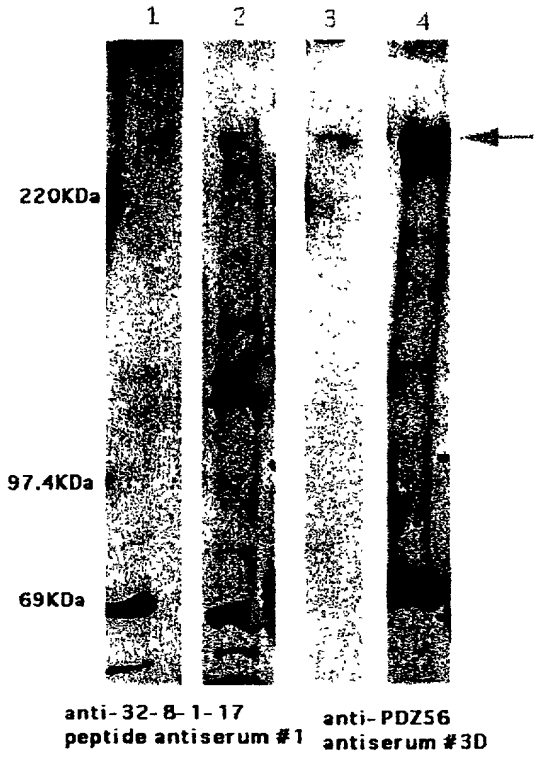
751 800
FH750
FH850 GAGATGCAAG CCATGAACAA GCTGTGGAAG CCATTCGGAA AGCAGGCAAC
FH950 GAGATGCAAG CCATGAACAA GCTGTGGAAG CCATTCGGAA AGCAGGCAAC
801 850
FH750
FH850 CCTGTAGTCT TTATGGTATA GAGCTTTATT ACAGACCAAG G
FH950 CCTGTAGTCT TTATGGTACA GAGCATTATA AACAGACCAA GGAAATCCCC
851 900
FH750
FH850
FH950 TTTGCCTTCC TTGCTGCACA ACCTTTACCC TAAGTACAAC TTCAGCAGCA
901 950
FH750 GCACCCAGT
FH850 GCACCCAGT
FH950 CTAACCCATT TGCTGACTCT CTACAAATCA ACGCCGACAA GGCACCCAGT
951 965
FH750 CAGTCAGAGT CAGAG
FH850 CAGTCAGAGT CAGAG
FH950 CAGTCAGAGT CAGAG

Figure 18

Figure 19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3
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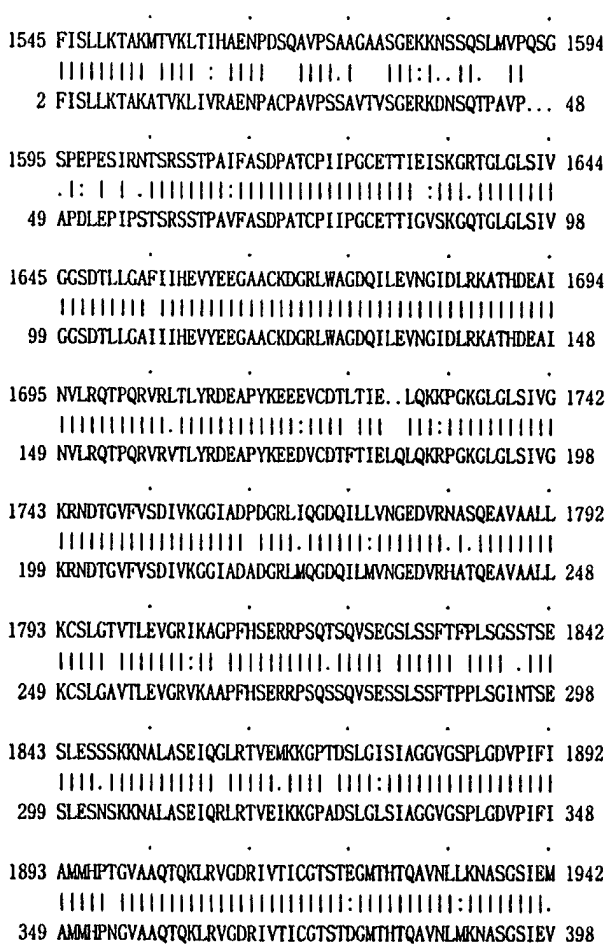
97.4KDa
69KDa
anti-32-8-1-17
peptide antiserum #1
anti-PDZ56
antiserum #3D



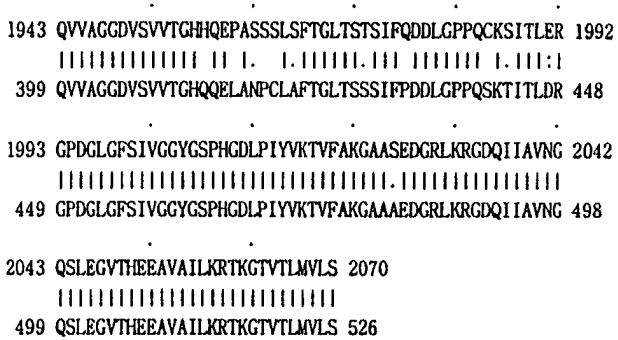


Figure 20

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1618 ATCPIIPGCETTIEISKGRTGLGLSIVGGSDTLLGAFIIHEVYEEGAACK 1667
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   1 ATCPIIPGCETTIEISKGRTGLGLSIVGGSDTLLGAIIIHEVYEEGAACK 50

1668 DGRLWAGDQILEVNGIDLRKATHDEAINVLRQTPQRVRLTLYRDEAPYKE 1717
     ||||||||||||||||||||||||||||||||||||||||||||||||||
  51 DGRLWAGDQILEVNGIDLRKATHDEAINVLRQTPQRVRLTLYRDEAPYKE 100

1718 EEVCDTLTIELQKKPGKGLGLSIVGKRNDTGVFVSDIVKGGIADPDGRLI 1767
     |||||||||||||||||||||||||||||||||||||||||||| ||||.
 101 EEVCDTLTIELQKKPGKGLGLSIVGKRNDTGVFVSDIVKGGIADADGRLM 150

1768 QGDQILLVNGEDVRNASQEAVAALLKCSLGTVTLEVGRIKAGPFHSERRP 1817
     ||||||:|||||||||.||||||||||||||||||||||||||||||||
 151 QGDQILMVNGEDVRNATQEAVAALLKCSLGTVTLEVGRIKAGPFHSERRP 200

1818 SQTSQVSEGSLSSFTFPLSGSSTSESLESSSKKNALASEIQGLRTVEMKK 1867
     ||.||||||||||||||||||||||||||||||||||||||||||||||||
 201 SQSSQVSEGSLSSFTFPLSGSSTSESLESSSKKNALASEIQGLRTVEMKK 250

1868 GPTDSLGISIAGGVGSPLGDVPIFIAMMHPTGVAAQTQKLRVGDRIVTIC 1917
     ||||||||||||||||||||||||||||||||||||||||||||||||||
 251 GPTDSLGISIAGGVGSPLGDVPIFIAMMHPTGVAAQTQKLRVGDRIVTIC 300

1918 GTSTEGMTHTQAVNLLKNASGSIEMQVVAGGDVSVVTGHHQEPASSSLSF 1967
     |||||||||||||||||||||||||||||||||| ||||||||||
 301 GTSTEGMTHTQAVNLLKNASGSIEMQVVAGGDVSVVTGHQQEPASSSLSF 350

1968 TGLTSTSIFQDDLGPPQCKSITLERGPDGLGFSIVGGYGSPHGDLPIYVK 2017
     |||||.||||||||||||||||||||||||||||||||||||||||||||
 351 TGLTSSSIFQDDLGPPQCKSITLERGPDGLGFSIVGGYGSPHGDLPIYVK 400

2018 TVFAKGAASEDGRLKRGDQIIAVNGQSLEGVTHEEAVAILKRTKGTVTLM 2067
     ||||||||||||||||||||||||||||||||||||||||||||||||||
 401 TVFAKGAASEDGRLKRGDQIIAVNGQSLEGVTHEEAVAILKRTKGTVTLM 450

2068 VLS 2070
     |||
 451 VLS 453
```

Figure 21

Figure 22

```
1 MLEAIDKNRALHAAERLQTKLRERGDVANEDKLSLLKSVLQSPLFSQILS 50
  ||| ||||||| |||||.||:||||||||||||||||||||||||||||
1 MLETIDKNRALQAAERLQSKLKERGDVANEDKLSLLKSVLQSPLFSQILS 50

51 LQTSVQQLKDQVNIATSATSNIEYAHVPHLSPAVIPTLQNESFLLSPNNG 100
   ||||.||||||||:|| ||.| ::|| |  | |:| ||.|| ||||.||
51 LQTSLQQLKDQVNVATLATANADHAHTPQFSSAIISNLQSESLLLSPSNG 100

101 NLEALTGPGI.PHINGKPACDEFDQLIKNMAQGRHVEVFELLKPPSGGLG 149
    ||||:.||| | ..|||||:| |||||.||||||||:||||||| ||||
101 NLEAISGPGAPPAMDGKPACEELDQLIKSMAQGRHVEIFELLKPPCGGLG 150

150 FSVVGLRSENRGELGIFVQEIQEGSVAHRDGRLKETDQILAINGQALDQT 199
    ||||||||||||||||||||||||||||||||||||||||||||| ||||
151 FSVVGLRSENRGELGIFVQEIQEGSVAHRDGRLKETDQILAINGQVLDQT 200

200 ITHQQAISILQKAKDTVQLVIARGSLPQLVSPIVSRSRSPSAASTISAHSNP 249
    |||||||||||||||:||||||||| : || :||||||||:||||||
201 ITHQQAISILQKAKDTIQLVIARGSLPHISSPRISRSRSPSAASTVSAHSNP 250

250 VHWQHMETIELVNDGSGLGFGIIGGKATGVIVKTILPGGVADQHGRLCSG 299
     ||||.||||||||||||||||||||||||||||||||||||||||||||
251 THWQHVETIELVNDGSGLGFGIIGGKATGVIVKTILPGGVADQHGRLCSG 300

300 DHILKIGDTDLAGMSSEQVAQVLRQCGNRVKLMIARSAIEERTAPTALGI 349
    |||||||||||||||||||||||||||||||||||| |:|| ||..|||
301 DHILKIGDTDLAGMSSEQVAQVLRQCGNRVKLMIARGAVEETPAPSSLGI 350

350 TLSSSPTSTPELRVDASTQKGEESETFDVELTKNVQGLGITIAGYIGDKK 399
    ||||| ||| |:|||||||| ||||||||||||||||||||||||||||
351 TLSSS.TSTSEMRVDASTQKNEESETFDVELTKNVQGLGITIAGYIGDKK 399

400 LEPSGIFVKSITKSSAVEHDGRIQIGDQIIAVDGTNLQGFTNQQAVEVLR 449
    ||||||||||||||||| |||||||||:||||||||||||||||||||
400 LEPSGIFVKSITKSSAVELDGRIQIGDQIVAVDGTNLQGFTNQQAVEVLR 449

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    |||||| |||||:| ||||: |||| || ||          ||||||:
450 HTGQTVRLTLMRKGASQEAEITSREDTAKDVDLP.......AENYEKDEE 492

500 FLSSTRNTNILPTEEEGYPLLSAEIEEIEDAQKQEAALLTKWQRIMGINY 549
     ||  |.|.||| |||||||| |:|| || | ||||||||||||||||
493 SLSLKRSTSILPIEEEGYPLLSTELEETEDVQ.QEAALLTKWQRIMGINY 541

550 EIVVAHVSKFSENSGLGISLEATVGHHFIRSVLPEGPVGHSGKLFSGDEL 599
    ||||||||||||||||||||||||||||||||||||||||||||||||||
542 EIVVAHVSKFSENSGLGISLEATVGHHFIRSVLPEGPVGHSGKLFSGDEL 591

600 LEVNGITLLGENHQDVVNILKELPIEVTMVCCRRTVPPTTQSELDSLDLC 649
    |||||| |||||||||||||||||:|||||||||||||  ||.||||:
592 LEVNGINLLGENHQDVVNILKELPIDVTMVCCRRTVPPTALSEVDSLDIH 641

650 DIELTEKPHVDLGEFIGSSEPEDPVLAMTDAGQSTEEVQAPLAMWEAGIQ 699
    |:|||||||:||||||||| |||.|||.|  |. ||:| |||||||||
642 DLELTEKPHIDLGEFIGSSETEDPMLAMSDVDQNAEEIQTPLAMWEAGIQ 691

700 HIMLEKGSKGLGFSILDYQDPIDPASTVIIIRSLVPGGIAEKDGRLLPGD 749
     | |||||:||||||||||||||||.|||:||||||||||||||||| |||
692 AIELEKGSRGLGFSILDYQDPIDPANTVIVIRSLVPGGIAEKDGRLFPGD 741

750 RLMFVNDVNLENSSLEEAVEALKGAPSGTVRIGVAKPLPLSPEEGYVSAK 799
    ||||||:|||||.||||||||||||||| ||||||||||||||||||||
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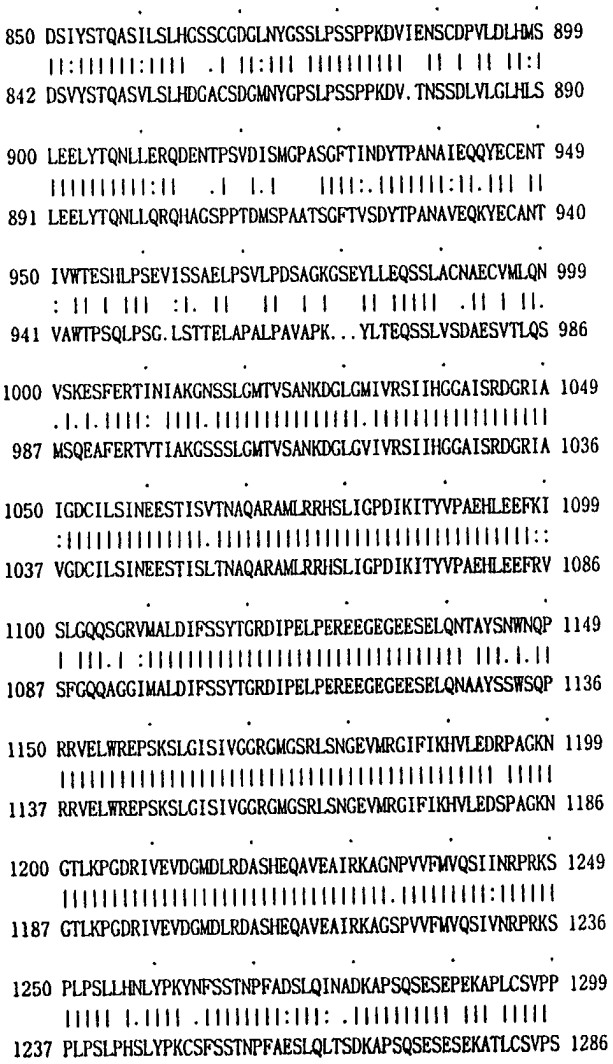

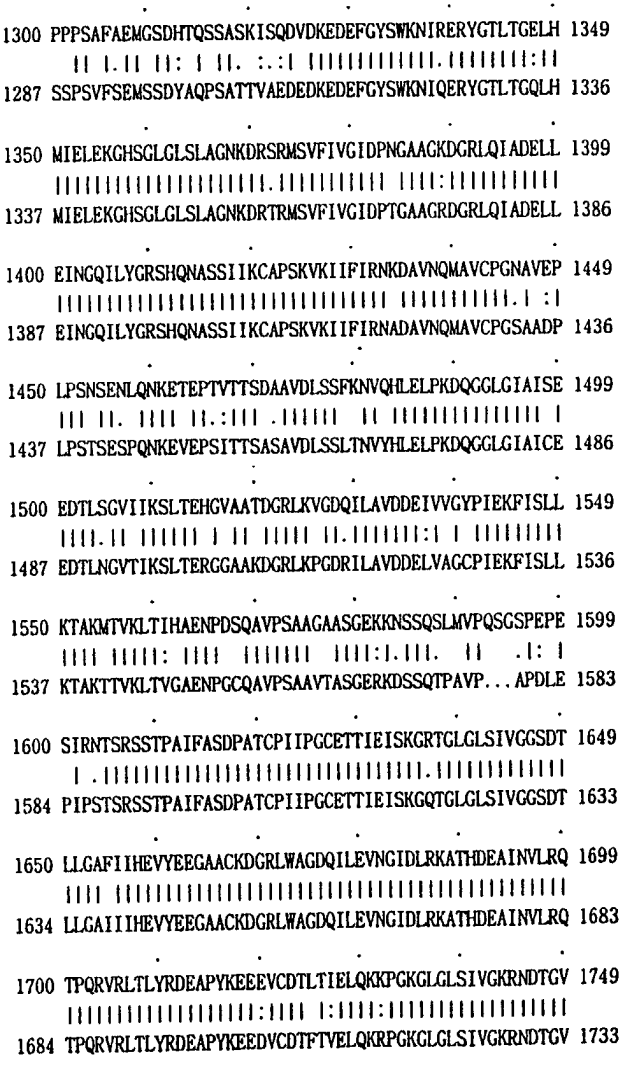

Figure 23

Figure 24

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Figure 25

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PDZ-C	SETFDVELTK	.N.VQGLGIT	IAGYIG....	.DKKLEPSGI	FVKSITKSSA
PDZ-D	YEIVVAHVSK	FSENSGLGIS	LEATVGHH..	....	FIRSVLPEGP
PDZ-E	AGIQHIMLEK	.G.SKGLGFS	ILDYQD....	.PIDPASTVI	IIRSLVPGGI
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PDZ-H	GELHMIELEK	.G.HSGLGLS	LAG.......	.NKDRSRMSV	FIVGIDPNGA
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PDZ-L	QGLRTVEMKK	.GPTDSLGIS	IAGGVG....	.SPLGDV.PI	FIAMMHPTGV
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	51				97
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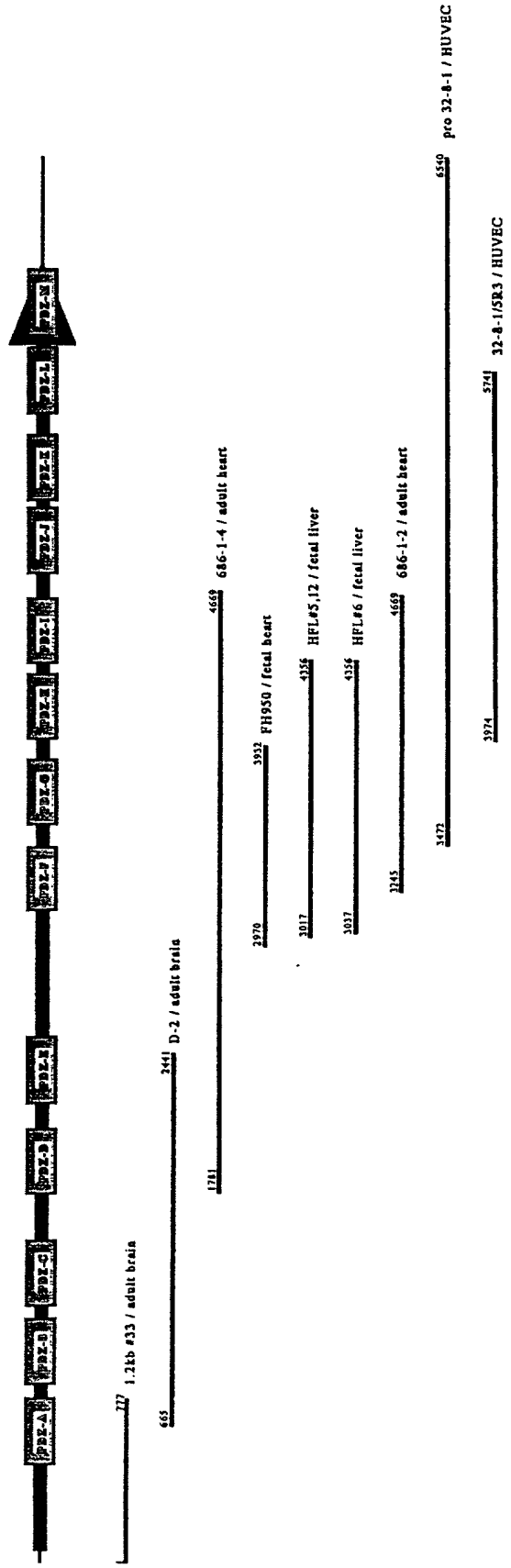
Figure 26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COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled PROTEIN HAVING PDZ DOMAIN SEQUENCE, the specification of which:

[X] is attached hereto.
[] was filed on _ as Application Serial No. _ and was amended on _____.
[] was described and claimed in PCT International Application No. _____ filed on _____ and as amended under PCT Article 19 on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Serial No.	Filing Date	Status
PCT/JP98/03603	August 12, 1998	Pending

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

Country	Application No.	Filing Date	Priority Claimed
Japan	9/230356	August 12, 1997	[X] Yes [] No
Japan	10/189944	June 19, 1998	[X] Yes [] No

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Janis K. Fraser, Reg. No. 34,819
J. Peter Fasse, Reg. No. 32,983
Timothy A. French, Reg. No. 30,175
Anita L. Meiklejohn, Reg. No. 35,283
Eldora L. Ellison, Reg. No. 39,967
John W. Freeman, Reg. No. 29,066
John T. Li, Reg. No. 40,210
Ralph A. Mittelberger, Reg. No. 33,195

Address all telephone calls to JANIS K. FRASER at telephone number (617) 542-5070.

Combined Declaration and Power of Attorney

Address all correspondence to JANIS K. FRASER at:

FISH & RICHARDSON P.C.
225 Franklin Street
Boston, MA 02110-2804

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Full Name of Inventor: SHIN-ICHI FUNAHASHI

Inventor's Signature: _____ Date: _____
Residence Address: 153-2, Nagai, Niihari-mura, Niihari-gun
Ibaraki 300-4101 Japan
Citizenship: Japan
Post Office Address: 153-2, Nagai, Niihari-mura, Niihari-gun
Ibaraki 300-4101 Japan

Full Name of Inventor: SHOJI MIYATA

Inventor's Signature: _____ Date: _____
Residence Address: 153-2, Nagai, Niihari-mura, Niihari-gun
Ibaraki 300-4101 Japan
Citizenship: Japan
Post Office Address: 153-2, Nagai, Niihari-mura, Niihari-gun
Ibaraki 300-4101 Japan

SEQUENCE LISTING

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Leu Asp Leu Cys Asp Ile Glu Leu Thr Glu Lys Pro His Val Asp Leu
     20                  25                  30

ggt gag ttc atc ggg tca tca gag aca gag gat cca gtg ctg gcg atg      441
Gly Glu Phe Ile Gly Ser Ser Glu Thr Glu Asp Pro Val Leu Ala Met
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act gat gcg ggt cag agt aca gaa gag gtt caa gca cct ttg gcc atg      489
Thr Asp Ala Gly Gln Ser Thr Glu Glu Val Gln Ala Pro Leu Ala Met
                 55                  60                  65

tgg gag gct ggc att cag cac ata gag ctg gag aaa ggg agc aaa gga      537
Trp Glu Ala Gly Ile Gln His Ile Glu Leu Glu Lys Gly Ser Lys Gly
            70                  75                  80

ctt ggt ttt agc att tta gat tat cag gat cca att gat cca gca agc      585
Leu Gly Phe Ser Ile Leu Asp Tyr Gln Asp Pro Ile Asp Pro Ala Ser
        85                  90                  95
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act gtg att ata att cgt tct ttg gtg cct ggc ggc att gct gaa aag 633
Thr Val Ile Ile Ile Arg Ser Leu Val Pro Gly Gly Ile Ala Glu Lys
100 105 110

gat gga cga ctt ctt cct ggt gac cga ctc atg ttt gta aac gat gtt 681
Asp Gly Arg Leu Leu Pro Gly Asp Arg Leu Met Phe Val Asn Asp Val
115 120 125 130

aac ttg gaa aac agc agt ctt gag gaa gct gta gaa gca ctg aag gga 729
Asn Leu Glu Asn Ser Ser Leu Glu Glu Ala Val Glu Ala Leu Lys Gly
135 140 145

gca ccg tca ggg act gtg aga ata gga gtt gct aag cct tta ccc ctt 777
Ala Pro Ser Gly Thr Val Arg Ile Gly Val Ala Lys Pro Leu Pro Leu
150 155 160

tca cca gaa gaa ggt tat gtt tct gct aag gag gat tcc ttt ctc tac 825
Ser Pro Glu Glu Gly Tyr Val Ser Ala Lys Glu Asp Ser Phe Leu Tyr
165 170 175

cca cca cac tcc tgt gag gaa gca ggg ctg gct gac aaa ccc ctc ttc 873
Pro Pro His Ser Cys Glu Glu Ala Gly Leu Ala Asp Lys Pro Leu Phe
180 185 190

agg gct gac ttg gct ctg gtg ggc aca aat gat gct gac tta gta gat 921
Arg Ala Asp Leu Ala Leu Val Gly Thr Asn Asp Ala Asp Leu Val Asp

195 200 205 210

gaa tcc aca ttt gag tct cca tac tct cct gaa aat gac agc atc tac 969
Glu Ser Thr Phe Glu Ser Pro Tyr Ser Pro Glu Asn Asp Ser Ile Tyr
215 220 225

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Ser Thr Gln Ala Ser Ile Leu Ser Leu His Gly Ser Ser Cys Gly Asp
230 235 240

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Gly Leu Asn Tyr Gly Ser Ser Leu Pro Ser Ser Pro Pro Lys Asp Val
245 250 255

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Ile Glu Asn Ser Cys Asp Pro Val Leu Asp Leu His Met Ser Leu Glu
260 265 270

gaa cta tat acc cag aat ctc ctg gaa aga cag gat gag aat aca cct 1161
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275 280 285 290

tcg gtg gac ata agt atg ggg cct gct tct ggc ttt act ata aat gac 1209
Ser Val Asp Ile Ser Met Gly Pro Ala Ser Gly Phe Thr Ile Asn Asp
295 300 305

tac aca cct gca aat gct att gaa caa caa tat gaa tgt gaa aac aca 1257

Tyr Thr Pro Ala Asn Ala Ile Glu Gln Gln Tyr Glu Cys Glu Asn Thr

310 315 320

ata gtg tgg act gaa tct cat tta cca agt gaa gtt ata tca agt gca 1305

Ile Val Trp Thr Glu Ser His Leu Pro Ser Glu Val Ile Ser Ser Ala

325 330 335

gaa ctt cct tct gtg cta ccc gat tca gct gga aag ggc tct gag cac 1353

Glu Leu Pro Ser Val Leu Pro Asp Ser Ala Gly Lys Gly Ser Glu His

340 345 350

ctg ctt gaa cag agc tcc ctg gcc tgt aat gct gag tgt gtc atg ctt 1401

Leu Leu Glu Gln Ser Ser Leu Ala Cys Asn Ala Glu Cys Val Met Leu

355 360 365 370

caa aat gta tct aaa gaa tct ttt gaa agg act att aat ata gca aaa 1449

Gln Asn Val Ser Lys Glu Ser Phe Glu Arg Thr Ile Asn Ile Ala Lys

375 380 385

ggc aat tct agc cta gga atg aca gtt agt gct aat aaa gat ggc ttg 1497

Gly Asn Ser Ser Leu Gly Met Thr Val Ser Ala Asn Lys Asp Gly Leu

390 395 400

ggg atg atc gtt cga agc att att cat gga ggt gcc att agt cga gat 1545

Gly Met Ile Val Arg Ser Ile Ile His Gly Gly Ala Ile Ser Arg Asp

405 410 415

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Gly Arg Ile Ala Ile Gly Asp Cys Ile Leu Ser Ile Asn Glu Glu Ser
420 425 430

acc atc agt gta acc aat gcc cag gca cga gct atg ttg aga aga cat 1641
Thr Ile Ser Val Thr Asn Ala Gln Ala Arg Ala Met Leu Arg Arg His
435 440 445 450

tct ctc att ggc cct gac ata aaa att act tat gtg cct gca gaa cat 1689
Ser Leu Ile Gly Pro Asp Ile Lys Ile Thr Tyr Val Pro Ala Glu His
455 460 465

ttg gaa gag ttc aaa ata agc ttg gga caa caa tct gga aga gta atg 1737
Leu Glu Glu Phe Lys Ile Ser Leu Gly Gln Gln Ser Gly Arg Val Met
470 475 480

gca ctg gat att ttt tct tca tac act ggc aga gac att cca gaa tta 1785
Ala Leu Asp Ile Phe Ser Ser Tyr Thr Gly Arg Asp Ile Pro Glu Leu
485 490 495

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Pro Glu Arg Glu Glu Gly Glu Gly Glu Glu Ser Glu Leu Gln Asn Thr
500 505 510

gca tat agc aat tgg aat cag ccc agg cgg gtg gaa ctc tgg aga gaa 1881
Ala Tyr Ser Asn Trp Asn Gln Pro Arg Arg Val Glu Leu Trp Arg Glu
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Pro Ser Lys Ser Leu Gly Ile Ser Ile Val Gly Gly Arg Gly Met Gly
535 540 545

agt cgg cta agc aat gga gaa gtg atg agg ggc att ttc atc aaa cat 1977
Ser Arg Leu Ser Asn Gly Glu Val Met Arg Gly Ile Phe Ile Lys His
550 555 560

gtt ctg gaa gat agt cca gct ggc aaa aat gga acc ttg aaa cct gga 2025
Val Leu Glu Asp Ser Pro Ala Gly Lys Asn Gly Thr Leu Lys Pro Gly
565 570 575

gat aga atc gta gag gca ccc agt cag tca gag tca gag cca gag aag 2073
Asp Arg Ile Val Glu Ala Pro Ser Gln Ser Glu Ser Glu Pro Glu Lys
580 585 590

gct cca ttg tgc agt gtg ccc cca ccc cct cct tca gcc ttt gcc gaa 2121
Ala Pro Leu Cys Ser Val Pro Pro Pro Pro Pro Ser Ala Phe Ala Glu
595 600 605 610

atg ggt agt gat cac aca cag tca tct gca agc aaa atc tca caa gat 2169
Met Gly Ser Asp His Thr Gln Ser Ser Ala Ser Lys Ile Ser Gln Asp
615 620 625

gtg gac aaa gag gat gag ttt ggt tac agc tgg aaa aat atc aga gag 2217
Val Asp Lys Glu Asp Glu Phe Gly Tyr Ser Trp Lys Asn Ile Arg Glu

630 635 640

cgt tat gga acc cta aca ggc gag ctg cat atg att gaa ctg gag aaa 2265
Arg Tyr Gly Thr Leu Thr Gly Glu Leu His Met Ile Glu Leu Glu Lys
645 650 655

ggt cat agt ggt ttg ggc cta agt ctt gct ggg aac aaa gac cga tcc 2313
Gly His Ser Gly Leu Gly Leu Ser Leu Ala Gly Asn Lys Asp Arg Ser
660 665 670

agg atg agt gtc ttc ata gtg ggg att gat cca aat gga gct gca gga 2361
Arg Met Ser Val Phe Ile Val Gly Ile Asp Pro Asn Gly Ala Ala Gly
675 680 685 690

aaa gat ggt cga ttg caa att gca gat gag ctt cta gag atc aat ggt 2409
Lys Asp Gly Arg Leu Gln Ile Ala Asp Glu Leu Leu Glu Ile Asn Gly
695 700 705

cag att tta tat gga aga agt cat cag aat gcc tca tca atc att aaa 2457
Gln Ile Leu Tyr Gly Arg Ser His Gln Asn Ala Ser Ser Ile Ile Lys
710 715 720

tgt gcc cct tct aaa gtg aaa ata att ttt atc aga aat aaa gat gca 2505
Cys Ala Pro Ser Lys Val Lys Ile Ile Phe Ile Arg Asn Lys Asp Ala
725 730 735

gtg aat cag atg gcc gta tgt cct gga aat gca gta gaa cct ttg cct 2553

Val Asn Gln Met Ala Val Cys Pro Gly Asn Ala Val Glu Pro Leu Pro
740 745 750

tct aac tca gaa aat ctt caa aat aag gag aca gag cca act gtt act 2601
Ser Asn Ser Glu Asn Leu Gln Asn Lys Glu Thr Glu Pro Thr Val Thr
755 760 765 770

act tct gat gca gct gtg gac ctc agt tca ttt aaa aat gtg caa cat 2649
Thr Ser Asp Ala Ala Val Asp Leu Ser Ser Phe Lys Asn Val Gln His
775 780 785

ctg gag ctt ccc aag gat cag ggg ggt ttg ggt att gct atc agc gaa 2697
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790 795 800

gaa gat aca ctc agt gga gtc atc ata aag agc tta aca gag cat ggg 2745
Glu Asp Thr Leu Ser Gly Val Ile Ile Lys Ser Leu Thr Glu His Gly
805 810 815

gta gca gcc acg gat gga cga ctc aaa gtc gga gat cag ata ctg gct 2793
Val Ala Ala Thr Asp Gly Arg Leu Lys Val Gly Asp Gln Ile Leu Ala
820 825 830

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Val Asp Asp Glu Ile Val Val Gly Tyr Pro Ile Glu Lys Phe Ile Ser
835 840 845 850

ctt ctg aag aca gca aag atg aca gta aaa ctt acc atc cat gct gag 2889
Leu Leu Lys Thr Ala Lys Met Thr Val Lys Leu Thr Ile His Ala Glu
855 860 865

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870 875 880

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Glu Lys Lys Asn Ser Ser Gln Ser Leu Met Val Pro Gln Ser Gly Ser
885 890 895

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Pro Glu Pro Glu Ser Ile Arg Asn Thr Ser Arg Ser Ser Thr Pro Ala
900 905 910

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915 920 925 930

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935 940 945

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Val Gly Gly Ser Asp Thr Leu Leu Gly Ala Phe Ile Ile His Glu Val
950 955 960

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965 970 975

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Gln Ile Leu Glu Val Asn Gly Ile Asp Leu Arg Lys Ala Thr His Asp
980 985 990

gaa gca atc aat gtc ctg aga cag acg cca cag aga gtg cgc ctg aca 3321
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Ile Val Gly Lys Arg Asn Asp Thr Gly Val Phe Val Ser Asp Ile Val
1045 1050 1055

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Lys Gly Gly Ile Ala Asp Pro Asp Gly Arg Leu Ile Gln Gly Asp Gln

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1075 1080 1085 1090

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1095 1100 1105

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Gly Arg Ile Lys Ala Gly Pro Phe His Ser Glu Arg Arg Pro Ser Gln
1110 1115 1120

acc agc cag gtg agt gaa ggc agc ctg tct tct ttc act ttt cca ctc 3705
Thr Ser Gln Val Ser Glu Gly Ser Leu Ser Ser Phe Thr Phe Pro Leu
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Ser Gly Ser Ser Thr Ser Glu Ser Leu Glu Ser Ser Ser Lys Lys Asn
1140 1145 1150

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Ala Leu Ala Ser Glu Ile Gln Gly Leu Arg Thr Val Glu Met Lys Lys
1155 1160 1165 1170

ggc cct act gac tca ctg gga atc agc atc gct gga gga gta ggc agc 3849

Gly Pro Thr Asp Ser Leu Gly Ile Ser Ile Ala Gly Gly Val Gly Ser

1175 1180 1185

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Pro Leu Gly Asp Val Pro Ile Phe Ile Ala Met Met His Pro Thr Gly

1190 1195 1200

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Val Ala Ala Gln Thr Gln Lys Leu Arg Val Gly Asp Arg Ile Val Thr

1205 1210 1215

atc tgt ggc aca tcc act gag ggc atg act cac acc caa gca gtt aac 3993

Ile Cys Gly Thr Ser Thr Glu Gly Met Thr His Thr Gln Ala Val Asn

1220 1225 1230

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Leu Leu Lys Asn Ala Ser Gly Ser Ile Glu Met Gln Val Val Ala Gly

1235 1240 1245 1250

gga gac gtg agt gtg gtc aca ggt cat cat cag gag cct gca agt tcc 4089

Gly Asp Val Ser Val Val Thr Gly His His Gln Glu Pro Ala Ser Ser

1255 1260 1265

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Ser Leu Ser Phe Thr Gly Leu Thr Ser Thr Ser Ile Phe Gln Asp Asp

1270 1275 1280

tta gga cct cct caa tgt aag tct att aca cta gag cga gga cca gat 4185
Leu Gly Pro Pro Gln Cys Lys Ser Ile Thr Leu Glu Arg Gly Pro Asp
1285 1290 1295

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Gly Leu Gly Phe Ser Ile Val Gly Gly Tyr Gly Ser Pro His Gly Asp
1300 1305 1310

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Leu Pro Ile Tyr Val Lys Thr Val Phe Ala Lys Gly Ala Ala Ser Glu
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Asp Gly Arg Leu Lys Arg Gly Asp Gln Ile Ile Ala Val Asn Gly Gln
1335 1340 1345

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1350 1355 1360

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1365 1370

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<213> Homo sapience

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20 25 30

Ile Ile Ile Arg Ser Leu Val Pro Gly Gly Ile Ala Glu Lys Asp Gly
35 40 45

Arg Leu Leu Pro Gly Asp Arg Leu Met Phe Val Asn Asp Val Asn Leu
50 55 60

Glu Asn Ser Ser Leu Glu Glu Ala Val Glu Ala Leu Lys Gly Ala Pro
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Ser Gly Thr Val Arg Ile Gly Val Ala Lys
85 90

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20 25 30
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35 40 45
Gly Arg Ile Ala Ile Gly Asp Cys Ile Leu Ser Ile Asn Glu Glu Ser
50 55 60
Thr Ile Ser Val Thr Asn Ala Gln Ala Arg Ala Met Leu Arg Arg His
65 70 75 80
Ser Leu Ile Gly Pro Asp Ile Lys Ile Thr Tyr
85 90

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20 25 30

Gly Glu Val Met Arg Gly Ile Phe Ile Lys His Val Leu Glu Asp Ser
35 40 45

Pro Ala Gly Lys Asn Gly Thr Leu Lys Pro Gly Asp Arg Ile Val Glu
50 55 60

Ala Pro Ser Gln Ser Glu Ser Glu Pro Glu Lys Ala Pro Leu Cys Ser
65 70 75 80

Val Pro Pro Pro Pro Pro Ser Ala Phe Ala Glu Met Gly Ser Asp His
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20 25 30

Val Gly Ile Asp Pro Asn Gly Ala Ala Gly Lys Asp Gly Arg Leu Gln

35 40 45

Ile Ala Asp Glu Leu Leu Glu Ile Asn Gly Gln Ile Leu Tyr Gly Arg

50 55 60

Ser His Gln Asn Ala Ser Ser Ile Ile Lys Cys Ala Pro Ser Lys Val

65 70 75 80

Lys Ile Ile Phe Ile Arg

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Ile Ala Ile Ser Glu Glu Asp Thr Leu Ser Gly Val Ile Ile Lys Ser

20 25 30

Leu Thr Glu His Gly Val Ala Ala Thr Asp Gly Arg Leu Lys Val Gly

35 40 45

Asp Gln Ile Leu Ala Val Asp Asp Glu Ile Val Val Gly Tyr Pro Ile

50 55 60

Glu Lys Phe Ile Ser Leu Leu Lys Thr Ala Lys Met Thr Val Lys Leu

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Thr Ile His Ala

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<211> 86

<212> PRT

<213> Homo sapience

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20 25 30
His Glu Val Tyr Glu Glu Gly Ala Ala Cys Lys Asp Gly Arg Leu Trp
35 40 45
Ala Gly Asp Gln Ile Leu Glu Val Asn Gly Ile Asp Leu Arg Lys Ala
50 55 60
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Asp Ile Val Lys Gly Gly Ile Ala Asp Pro Asp Gly Arg Leu Ile Gln
        35                  40                  45
Gly Asp Gln Ile Leu Leu Val Asn Gly Glu Asp Val Arg Asn Ala Ser
    50                  55                  60
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            20                  25                  30
Ile Phe Ile Ala Met Met His Pro Thr Gly Val Ala Ala Gln Thr Gln
        35                  40                  45
Lys Leu Arg Val Gly Asp Arg Ile Val Thr Ile Cys Gly Thr Ser Thr
    50                  55                  60
Glu Gly Met Thr His Thr Gln Ala Val Asn Leu Leu Lys Asn Ala Ser
65                  70                  75                  80
Gly Ser Ile Glu Met Gln Val Val Ala
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85

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20 25 30

Tyr Val Lys Thr Val Phe Ala Lys Gly Ala Ala Ser Glu Asp Gly Arg
35 40 45

Leu Lys Arg Gly Asp Gln Ile Ile Ala Val Asn Gly Gln Ser Leu Glu
50 55 60

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Thr Val Thr Leu Met Val Leu Ser
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<211> 184

<212> DNA

<213> Homo sapience

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<210> 15

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<400> 15

ctctgactct gactgactgg 20

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tcagagagcg ttatggaacc 20

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<212> DNA

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<212> DNA

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<212> DNA

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gttgtttcgc agccagggat 20

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His Thr Gln Ser Ser Ala Ser Lys Ile Ser Gln Asp Val Asp Lys Glu
5 10 15 20

gat gag ttt ggt tac agc tgg aaa aat atc aga gag cgt tat gga acc 150
Asp Glu Phe Gly Tyr Ser Trp Lys Asn Ile Arg Glu Arg Tyr Gly Thr
25 30 35

cta aca ggc gag ctg cat atg att gaa ctg gag aaa ggt cat agt ggt 198
Leu Thr Gly Glu Leu His Met Ile Glu Leu Glu Lys Gly His Ser Gly
40 45 50

ttg ggc cta agt ctt gct ggg aac aaa gac cga tcc agg atg agt gtc 246
Leu Gly Leu Ser Leu Ala Gly Asn Lys Asp Arg Ser Arg Met Ser Val
55 60 65

ttc ata gtg ggg att gat cca aat gga gct gca gga aaa gat ggt cga 294
Phe Ile Val Gly Ile Asp Pro Asn Gly Ala Ala Gly Lys Asp Gly Arg
70 75 80

ttg caa att gca gat gag ctt cta gag atc aat ggt cag att tta tat 342
Leu Gln Ile Ala Asp Glu Leu Leu Glu Ile Asn Gly Gln Ile Leu Tyr
85 90 95 100

gga aga agt cat cag aat gcc tca tca atc att aaa tgt gcc cct tct 390
Gly Arg Ser His Gln Asn Ala Ser Ser Ile Ile Lys Cys Ala Pro Ser

105 110 115

aaa gtg aaa ata att ttt atc aga aat aaa gat gca gtg aat cag atg 438
Lys Val Lys Ile Ile Phe Ile Arg Asn Lys Asp Ala Val Asn Gln Met
120 125 130

gcc gta tgt cct gga aat gca gta gaa cct ttg cct tct aac tca gaa 486
Ala Val Cys Pro Gly Asn Ala Val Glu Pro Leu Pro Ser Asn Ser Glu
135 140 145

aat ctt caa aat aag gag cca gag cca act gtt act act tct gat gca 534
Asn Leu Gln Asn Lys Glu Pro Glu Pro Thr Val Thr Thr Ser Asp Ala
150 155 160

gct gtg gac ctc agt tca ttt aaa aat gtg caa cat ctg gag ctt ccc 582
Ala Val Asp Leu Ser Ser Phe Lys Asn Val Gln His Leu Glu Leu Pro
165 170 175 180

aag gat cag ggg ggt ttg ggt att gct atc agc gaa gaa gat aca ctc 630
Lys Asp Gln Gly Gly Leu Gly Ile Ala Ile Ser Glu Glu Asp Thr Leu
185 190 195

agt gga gtc atc ata aag agc tta aca gag cat ggg gta gca gcc acg 678
Ser Gly Val Ile Ile Lys Ser Leu Thr Glu His Gly Val Ala Ala Thr
200 205 210

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Asp Gly Arg Leu Lys Val Gly Asp Gln Ile Leu Ala Val Asp Asp Glu

215 220 225

att gtt gtt ggt tac cct att gaa aag ttt att agc ctt ctg aag aca 774

Ile Val Val Gly Tyr Pro Ile Glu Lys Phe Ile Ser Leu Leu Lys Thr

230 235 240

gca aag atg aca gta aaa ctt acc atc cat gct gag aat cca gat tcc 822

Ala Lys Met Thr Val Lys Leu Thr Ile His Ala Glu Asn Pro Asp Ser

245 250 255 260

cag gct gtt cct tca gca gct ggt gca gcc agt gga gaa aaa aag aac 870

Gln Ala Val Pro Ser Ala Ala Gly Ala Ala Ser Gly Glu Lys Lys Asn

265 270 275

agc tcc cag tct ctg atg gtc cca cag tct ggc tcc cca gaa ccg gag 918

Ser Ser Gln Ser Leu Met Val Pro Gln Ser Gly Ser Pro Glu Pro Glu

280 285 290

tcc atc cga aat aca agc aga tca tca aca cca gca att ttt gct tct 966

Ser Ile Arg Asn Thr Ser Arg Ser Ser Thr Pro Ala Ile Phe Ala Ser

295 300 305

gat cct gca acc tgc ccc att atc cct ggc tgc gaa aca acc atc gag 1014

Asp Pro Ala Thr Cys Pro Ile Ile Pro Gly Cys Glu Thr Thr Ile Glu

310 315 320

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325                 330                 335                 340

gac acg ctg ctg ggt gcc ttt att atc cat gaa gtt tat gaa gaa gga     1110
Asp Thr Leu Leu Gly Ala Phe Ile Ile His Glu Val Tyr Glu Glu Gly
                345                 350                 355

gca gca tgt aaa gat gga aga ctc tgg gct gga gat cag atc tta gag     1158
Ala Ala Cys Lys Asp Gly Arg Leu Trp Ala Gly Asp Gln Ile Leu Glu
            360                 365                 370

gtg aat gga att gac ttg agg aag gcc aca cat gat gaa gca atc aat     1206
Val Asn Gly Ile Asp Leu Arg Lys Ala Thr His Asp Glu Ala Ile Asn
        375                 380                 385

gtc ctg aga cag acg cca cag aga gtg cgc ctg aca ctc tac aga gat     1254
Val Leu Arg Gln Thr Pro Gln Arg Val Arg Leu Thr Leu Tyr Arg Asp
    390                 395                 400

gag gcc cca tac aaa gag gag gaa gtg tgt gac acc ctc act att gag     1302
Glu Ala Pro Tyr Lys Glu Glu Glu Val Cys Asp Thr Leu Thr Ile Glu
405                 410                 415                 420

ctg cag aag aag ccg gga aaa ggc cta gga tta agt att gtt ggt aaa     1350
Leu Gln Lys Lys Pro Gly Lys Gly Leu Gly Leu Ser Ile Val Gly Lys
                425                 430                 435
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440 445 450

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Ala Asp Pro Asp Gly Arg Leu Ile Gln Gly Asp Gln Ile Leu Leu Val
455 460 465

aat ggg gaa gac gtt cgt aat gcc tcc caa gaa gcg gtt gcc gct ttg 1494
Asn Gly Glu Asp Val Arg Asn Ala Ser Gln Glu Ala Val Ala Ala Leu
470 475 480

cta aag tgt tcc cta ggc aca gta acc ttg gaa gtt gga aga atc aaa 1542
Leu Lys Cys Ser Leu Gly Thr Val Thr Leu Glu Val Gly Arg Ile Lys
485 490 495 500

gct ggt cca ttc cat tca gag agg agg cca tct caa acc agc cag gtg 1590
Ala Gly Pro Phe His Ser Glu Arg Arg Pro Ser Gln Thr Ser Gln Val
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Ser Glu Gly Ser Leu Ser Ser Phe Thr Phe Pro Leu Ser Gly Ser Ser
520 525 530

aca tct gag tca ctg gaa agt agc tca aag aag aat gca ttg gca tct 1686
Thr Ser Glu Ser Leu Glu Ser Ser Ser Lys Lys Asn Ala Leu Ala Ser

535 540 545

gaa ata cag gga tta aga aca gtc gaa atg aaa aag ggc cct act gac 1734
Glu Ile Gln Gly Leu Arg Thr Val Glu Met Lys Lys Gly Pro Thr Asp
550 555 560

tca ctg gga atc agc atc gct gga gga gta ggc agc cca ctt ggt gat 1782
Ser Leu Gly Ile Ser Ile Ala Gly Gly Val Gly Ser Pro Leu Gly Asp
565 570 575 580

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Val Pro Ile Phe Ile Ala Met Met His Pro Thr Gly Val Ala Ala Gln
585 590 595
acc caa aaa ctc aga gtt ggg gat agg att gtc acc atc tgt ggc aca 1878
Thr Gln Lys Leu Arg Val Gly Asp Arg Ile Val Thr Ile Cys Gly Thr
600 605 610

tcc act gag ggc atg act cac acc caa gca gtt aac cta ctg aaa aat 1926
Ser Thr Glu Gly Met Thr His Thr Gln Ala Val Asn Leu Leu Lys Asn
615 620 625

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Ala Ser Gly Ser Ile Glu Met Gln Val Val Ala Gly Gly Asp Val Ser
630 635 640

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Val Val Thr Gly His His Gln Glu Pro Ala Ser Ser Ser Leu Ser Phe

645 650 655 660

act ggg ctg acg tca acc agt ata ttt cag gat gat tta gga cct cct 2070
Thr Gly Leu Thr Ser Thr Ser Ile Phe Gln Asp Asp Leu Gly Pro Pro
665 670 675

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Gln Cys Lys Ser Ile Thr Leu Glu Arg Gly Pro Asp Gly Leu Gly Phe
680 685 690

agt ata gtt gga gga tat ggc agc cct cat gga gac tta ccc att tat 2166
Ser Ile Val Gly Gly Tyr Gly Ser Pro His Gly Asp Leu Pro Ile Tyr
695 700 705

gtt aaa aca gtg ttt gca aag gga gca gcc tct gaa gac gga cgt ctg 2214
Val Lys Thr Val Phe Ala Lys Gly Ala Ala Ser Glu Asp Gly Arg Leu
710 715 720

aaa agg ggc gat cag atc att gct gtc aat ggg cag agt cta gaa gga 2262
Lys Arg Gly Asp Gln Ile Ile Ala Val Asn Gly Gln Ser Leu Glu Gly
725 730 735 740

gtc acc cat gaa gaa gct gtt gcc atc ctt aaa cgg aca aaa ggc act 2310
Val Thr His Glu Glu Ala Val Ala Ile Leu Lys Arg Thr Lys Gly Thr
745 750 755

gtc act ttg atg gtt ctc tct tgaattggct gccagaattg aaccaaccca 2361

Val Thr Leu Met Val Leu Ser

760

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Thr Val Gln Leu Val Ile Ala Arg Gly Ser Leu Pro Gln Leu Val Ser
                20                  25                  30

ccc ata gtt tcc cgt tct cca tct gca gcc agc aca att tca gct cac         143
Pro Ile Val Ser Arg Ser Pro Ser Ala Ala Ser Thr Ile Ser Ala His
            35                  40                  45

tct aat ccg gtt cac tgg caa cac atg gaa acg att gaa ttg gtg aat         191
Ser Asn Pro Val His Trp Gln His Met Glu Thr Ile Glu Leu Val Asn
        50                  55                  60

gat gga tct ggt ttg gga ttt ggc atc ata gga gga aaa gca act ggt         239
Asp Gly Ser Gly Leu Gly Phe Gly Ile Ile Gly Gly Lys Ala Thr Gly
    65                  70                  75

gtg ata gta aaa acc att ctg cct gga gga gta gct gat cag cat ggg         287
Val Ile Val Lys Thr Ile Leu Pro Gly Gly Val Ala Asp Gln His Gly
80                  85                  90                  95
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100 105 110

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Ala Gly Met Ser Ser Glu Gln Val Ala Gln Val Leu Arg Gln Cys Gly
115 120 125

aat aga gtt aag ttg atg att gca aga agt gcc ata gaa gaa cgt aca 431
Asn Arg Val Lys Leu Met Ile Ala Arg Ser Ala Ile Glu Glu Arg Thr
130 135 140

gca ccc act gct ttg ggc atc acc ctc tcc tca tcc cca act tca acg 479
Ala Pro Thr Ala Leu Gly Ile Thr Leu Ser Ser Ser Pro Thr Ser Thr
145 150 155

cca gag ttg cgg gtt gat gct tct act cag aaa ggt gaa gaa agt gag 527
Pro Glu Leu Arg Val Asp Ala Ser Thr Gln Lys Gly Glu Glu Ser Glu
160 165 170 175

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Thr Phe Asp Val Glu Leu Thr Lys Asn Val Gln Gly Leu Gly Ile Thr
180 185 190

att gct ggc tac att gga gat aaa aaa ttg gaa cct tca gga atc ttt 623
Ile Ala Gly Tyr Ile Gly Asp Lys Lys Leu Glu Pro Ser Gly Ile Phe

195 200 205

gta aag agc att aca aaa agc agt gcc gtt gag cat gat gga aga atc 671
Val Lys Ser Ile Thr Lys Ser Ser Ala Val Glu His Asp Gly Arg Ile
210 215 220

caa att gga gac caa att ata gca gta gat ggc aca aac ctt cag ggt 719
Gln Ile Gly Asp Gln Ile Ile Ala Val Asp Gly Thr Asn Leu Gln Gly
225 230 235

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Phe Thr Asn Gln Gln Ala Val Glu Val Leu Arg His Thr Gly Gln Thr
240 245 250 255

gtg ctc ctg aca cta atg agg aga gga atg aag cag gaa gcc gag ctc 815
Val Leu Leu Thr Leu Met Arg Arg Gly Met Lys Gln Glu Ala Glu Leu
260 265 270

atg tca agg gaa gac gtc aca aaa gat gca gat ttg tct cct gtt aat 863
Met Ser Arg Glu Asp Val Thr Lys Asp Ala Asp Leu Ser Pro Val Asn
275 280 285

gcc agc ata atc aaa gaa aat tat gaa aaa gat gaa gat ttt tta tct 911
Ala Ser Ile Ile Lys Glu Asn Tyr Glu Lys Asp Glu Asp Phe Leu Ser
290 295 300

tcg acg aga aac acc aac ata tta cca act gaa gaa gaa ggg tat cca 959

Ser Thr Arg Asn Thr Asn Ile Leu Pro Thr Glu Glu Glu Gly Tyr Pro
305 310 315

tta ctg tca gct gag ata gaa gaa ata gaa gat gca caa aaa caa gaa 1007
Leu Leu Ser Ala Glu Ile Glu Glu Ile Glu Asp Ala Gln Lys Gln Glu
320 325 330 335

gct gct ctg ctg aca aaa tgg caa agg att atg gga att aac tat gaa 1055
Ala Ala Leu Leu Thr Lys Trp Gln Arg Ile Met Gly Ile Asn Tyr Glu
340 345 350

ata gtg gtg gcc cat gtg agc aag ttt agt gag aac agt gga ttg ggg 1103
Ile Val Val Ala His Val Ser Lys Phe Ser Glu Asn Ser Gly Leu Gly
355 360 365

ata agc ctg gaa gcg aca gtg gga cat cat ttt atc cga tct gtt cta 1151
Ile Ser Leu Glu Ala Thr Val Gly His His Phe Ile Arg Ser Val Leu
370 375 380

cca gag ggt cct gtt gga cac agc ggg aag ctc ttc agt gga gac gag 1199
Pro Glu Gly Pro Val Gly His Ser Gly Lys Leu Phe Ser Gly Asp Glu
385 390 395

cta ttg gaa gta aat ggc ata act tta ctt ggg gaa aat cac caa gat 1247
Leu Leu Glu Val Asn Gly Ile Thr Leu Leu Gly Glu Asn His Gln Asp
400 405 410 415

gtg gtg aat atc tta aaa gaa ctg cct ata gaa gtg aca atg gtg tgc 1295
Val Val Asn Ile Leu Lys Glu Leu Pro Ile Glu Val Thr Met Val Cys
420 425 430

tgt cgt cga act gtg cca ccc acc acc caa tca gaa ttg gat agc ctg 1343
Cys Arg Arg Thr Val Pro Pro Thr Thr Gln Ser Glu Leu Asp Ser Leu
435 440 445

gac tta tgt gat att gag cta aca gaa aag cct cac gta gat cta ggt 1391
Asp Leu Cys Asp Ile Glu Leu Thr Glu Lys Pro His Val Asp Leu Gly
450 455 460

gag ttc atc ggg tca tca gag cca gag gat cca gtg ctg gcg atg act 1439
Glu Phe Ile Gly Ser Ser Glu Pro Glu Asp Pro Val Leu Ala Met Thr
465 470 475

gat gcg ggt cag agt aca gaa gag gtt caa gca cct ttg gcc atg tgg 1487
Asp Ala Gly Gln Ser Thr Glu Glu Val Gln Ala Pro Leu Ala Met Trp
480 485 490 495

gag gct ggc att cag cac ata atg ctg gag aaa ggg agc aaa gga ctt 1535
Glu Ala Gly Ile Gln His Ile Met Leu Glu Lys Gly Ser Lys Gly Leu
500 505 510

ggt ttt agc att tta gat tat cag gat cca att gat cca gca agc act 1583
Gly Phe Ser Ile Leu Asp Tyr Gln Asp Pro Ile Asp Pro Ala Ser Thr
515 520 525

gtg att ata att cgt tct ttg gtg cct ggc ggc att gct gaa aag gat 1631
Val Ile Ile Ile Arg Ser Leu Val Pro Gly Gly Ile Ala Glu Lys Asp
530 535 540

gga cga ctt ctt cct ggt gac cga ctc atg ttt gta aac gat gtt aac 1679
Gly Arg Leu Leu Pro Gly Asp Arg Leu Met Phe Val Asn Asp Val Asn
545 550 555

ttg gaa aac agc agt ctt gag gaa gct gta gaa gca ctg aag gga gca 1727
Leu Glu Asn Ser Ser Leu Glu Glu Ala Val Glu Ala Leu Lys Gly Ala
560 565 570 575

ccg tca ggg act gtg aga ata gga gtt gct aag cct tta ccc ctt tc 1774
Pro Ser Gly Thr Val Arg Ile Gly Val Ala Lys Pro Leu Pro Leu
580 585 590

ac 1776

<210> 76

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Artificially Synthesized Primer Sequence

<400> 76

gcagatggag aacgggaaac tatgg 76

<210> 77

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Artificially Synthesized Primer Sequence

<400> 77

gaacgggaaa ctatggggct gacaa 25

<210> 78

<211> 777

<212> DNA

<213> Homo sapience

<400> 78

ttctcagtca cgcagttcca ttttaattgc tgttaatcat ttcagagaag aacactgaac 60

tttgaaaaaa atg ttg gaa gcc att gac aaa aat cgg gcc ctg cat gca 109

Met Leu Glu Ala Ile Asp Lys Asn Arg Ala Leu His Ala

1 5 10

gca gag cgc ttg caa acc aag ctg cga gaa cgt ggg gat gta gca aat 157
Ala Glu Arg Leu Gln Thr Lys Leu Arg Glu Arg Gly Asp Val Ala Asn
15 20 25

gaa gac aaa ctg agc ctt ctg aag tca gtc ctg cag agc cct ctc ttc 205
Glu Asp Lys Leu Ser Leu Leu Lys Ser Val Leu Gln Ser Pro Leu Phe
30 35 40 45

agt cag att ctg agc ctt cag act tct gta cag cag ctg aaa gac cag 253
Ser Gln Ile Leu Ser Leu Gln Thr Ser Val Gln Gln Leu Lys Asp Gln
50 55 60

gta aat att gca act tca gca act tca aat att gaa tat gcc cac gtt 301
Val Asn Ile Ala Thr Ser Ala Thr Ser Asn Ile Glu Tyr Ala His Val
65 70 75

cct cat ctc agc cca gct gtg att cct act ctg caa aat gaa tcg ttt 349
Pro His Leu Ser Pro Ala Val Ile Pro Thr Leu Gln Asn Glu Ser Phe
80 85 90

tta tta tcc cca aac aat ggg aat ctg gaa gca ctt aca gga cct ggt 397
Leu Leu Ser Pro Asn Asn Gly Asn Leu Glu Ala Leu Thr Gly Pro Gly
95 100 105

att cca cac att aat ggg aaa cct gct tgt gat gaa ttt gat cag ctt 445
Ile Pro His Ile Asn Gly Lys Pro Ala Cys Asp Glu Phe Asp Gln Leu
110 115 120 125

atc aaa aat atg gcc cag ggt cgc cat gta gaa gtt ttt gag ctc ctc 493
Ile Lys Asn Met Ala Gln Gly Arg His Val Glu Val Phe Glu Leu Leu
130 135 140

aaa cct cca tct gga ggc ctt ggg ttt agt gtt gtg gga cta aga agt 541
Lys Pro Pro Ser Gly Gly Leu Gly Phe Ser Val Val Gly Leu Arg Ser
145 150 155

gaa aac aga gga gag ctg gga ata ttt gtt caa gag ata caa gag ggc 589
Glu Asn Arg Gly Glu Leu Gly Ile Phe Val Gln Glu Ile Gln Glu Gly
160 165 170

agt gtg gcc cat aga gat gga aga ttg aaa gaa act gat caa att ctt 637
Ser Val Ala His Arg Asp Gly Arg Leu Lys Glu Thr Asp Gln Ile Leu
175 180 185

gct atc aat gga cag gct ctt gat cag aca att aca cat cag cag gct 685
Ala Ile Asn Gly Gln Ala Leu Asp Gln Thr Ile Thr His Gln Gln Ala
190 195 200 205

atc agc atc ctg cag aaa gcc aaa gat act gtc cag cta gtt att gcc 733
Ile Ser Ile Leu Gln Lys Ala Lys Asp Thr Val Gln Leu Val Ile Ala
210 215 220

aga ggc tca ttg cct cag ctt gtc agc ccc ata gtt tcc cgt 775
Arg Gly Ser Leu Pro Gln Leu Val Ser Pro Ile Val Ser Arg

225 230 235

tc 777

<210> 79

<211> 755

<212> DNA

<213> Homo sapience

<400> 79

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Pro Ser Val Leu Pro Asp Ser Ala Gly Lys Gly Ser Glu Tyr Leu

1 5 10 15

ctt gaa cag agc tcc ctg gcc tgt aat gct gag tgt gtc atg ctt caa 95

Leu Glu Gln Ser Ser Leu Ala Cys Asn Ala Glu Cys Val Met Leu Gln

20 25 30

aat gta tct aaa gaa tct ttt gaa agg act att aat ata gca aaa ggc 143

Asn Val Ser Lys Glu Ser Phe Glu Arg Thr Ile Asn Ile Ala Lys Gly

35 40 45

aat tct agc cta gga atg aca gtt agt gct aat aaa gat ggc ttg ggg 191

Asn Ser Ser Leu Gly Met Thr Val Ser Ala Asn Lys Asp Gly Leu Gly

50 55 60

atg atc gtt cga agc att att cat gga ggt gcc att agt cga gat ggc 239
Met Ile Val Arg Ser Ile Ile His Gly Gly Ala Ile Ser Arg Asp Gly
65 70 75

cgg att gcc att ggg gac tgc atc ttg tcc att aat gaa gag tct acc 287
Arg Ile Ala Ile Gly Asp Cys Ile Leu Ser Ile Asn Glu Glu Ser Thr
80 85 90 95

atc agt gta acc aat gcc cag gca cga gct atg ttg aga aga cat tct 335
Ile Ser Val Thr Asn Ala Gln Ala Arg Ala Met Leu Arg Arg His Ser
100 105 110

ctc att ggc cct gac ata aaa att act tat gtg cct gca gaa cat ttg 383
Leu Ile Gly Pro Asp Ile Lys Ile Thr Tyr Val Pro Ala Glu His Leu
115 120 125

gaa gag ttc aaa ata agc ttg gga caa caa tct gga aga gta atg gca 431
Glu Glu Phe Lys Ile Ser Leu Gly Gln Gln Ser Gly Arg Val Met Ala
130 135 140

ctg gat att ttt tct tca tac act ggc aga gac att cca gaa tta cca 479
Leu Asp Ile Phe Ser Ser Tyr Thr Gly Arg Asp Ile Pro Glu Leu Pro
145 150 155

gag cga gaa gag gga gag ggt gaa gaa agc gaa ctt caa aac aca gca 527
Glu Arg Glu Glu Gly Glu Gly Glu Glu Ser Glu Leu Gln Asn Thr Ala
160 165 170 175

tat agc aat tgg aat cag ccc agg cgg gtg gaa ctc tgg aga gaa cca 575
Tyr Ser Asn Trp Asn Gln Pro Arg Arg Val Glu Leu Trp Arg Glu Pro
180 185 190

agc aaa tcc tta ggc atc agc att gtt ggt gga cga ggg atg ggg agt 623
Ser Lys Ser Leu Gly Ile Ser Ile Val Gly Gly Arg Gly Met Gly Ser
195 200 205

cgg cta agc aat gga gaa gtg atg agg ggc att ttc atc aaa cat gtt 671
Arg Leu Ser Asn Gly Glu Val Met Arg Gly Ile Phe Ile Lys His Val
210 215 220

ctg gaa gat agt cca gct ggc aaa aat gga acc ttg aaa cct gga gat 719
Leu Glu Asp Ser Pro Ala Gly Lys Asn Gly Thr Leu Lys Pro Gly Asp
225 230 235

aga atc gta gag gca ccc agt cag tca gag tca gag 755
Arg Ile Val Glu Ala Pro Ser Gln Ser Glu Ser Glu
240 245 250

<210> 80

<211> 865

<212> DNA

<213> Homo sapience

<400> 80

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     1               5                  10                  15

ctt gaa cag agc tcc ctg gcc tgt aat gct gag tgt gtc atg ctt caa          95
Leu Glu Gln Ser Ser Leu Ala Cys Asn Ala Glu Cys Val Met Leu Gln
                20                  25                  30

aat gta tct aaa gaa tct ttt gaa agg act att aat ata gca aaa ggc         143
Asn Val Ser Lys Glu Ser Phe Glu Arg Thr Ile Asn Ile Ala Lys Gly
            35                  40                  45

aat tct agc cta gga atg aca gtt agt gct aat aaa gat ggc ttg ggg         191
Asn Ser Ser Leu Gly Met Thr Val Ser Ala Asn Lys Asp Gly Leu Gly
        50                  55                  60

atg atc gtt cga agc att att cat gga ggt gcc att agt cga gat ggc         239
Met Ile Val Arg Ser Ile Ile His Gly Gly Ala Ile Ser Arg Asp Gly
    65                  70                  75

cgg att gcc att ggg gac tgc atc ttg tcc att aat gaa gag tct acc         287
Arg Ile Ala Ile Gly Asp Cys Ile Leu Ser Ile Asn Glu Glu Ser Thr
80                  85                  90                  95

atc agt gta acc aat gcc cag gca cga gct atg ttg aga aga cat tct         335
Ile Ser Val Thr Asn Ala Gln Ala Arg Ala Met Leu Arg Arg His Ser
                100                 105                 110
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ctc att ggc cct gac ata aaa att act tat gtg cct gca gaa cat ttg 383
Leu Ile Gly Pro Asp Ile Lys Ile Thr Tyr Val Pro Ala Glu His Leu
115 120 125

gaa gag ttc aaa ata agc ttg gga caa caa tct gga aga gta atg gca 431
Glu Glu Phe Lys Ile Ser Leu Gly Gln Gln Ser Gly Arg Val Met Ala
130 135 140

ctg gat att ttt tct tca tac act ggc aga gac att cca gaa tta cca 479
Leu Asp Ile Phe Ser Ser Tyr Thr Gly Arg Asp Ile Pro Glu Leu Pro
145 150 155

gag cga gaa gag gga gag ggt gaa gaa agc gaa ctt caa aac aca gca 527
Glu Arg Glu Glu Gly Glu Gly Glu Glu Ser Glu Leu Gln Asn Thr Ala
160 165 170 175

tat agc aat tgg aat cag ccc agg cgg gtg gaa ctc tgg aga gaa cca 575
Tyr Ser Asn Trp Asn Gln Pro Arg Arg Val Glu Leu Trp Arg Glu Pro
180 185 190

agc aaa tcc tta ggc atc agc att gtt ggt gga cga ggg atg ggg agt 623
Ser Lys Ser Leu Gly Ile Ser Ile Val Gly Gly Arg Gly Met Gly Ser
195 200 205

cgg cta agc aat gga gaa gtg atg agg ggc att ttc atc aaa cat gtt 671
Arg Leu Ser Asn Gly Glu Val Met Arg Gly Ile Phe Ile Lys His Val

210 215 220

ctg gaa gat agt cca gct ggc aaa aat gga acc ttg aaa cct gga gat 719
Leu Glu Asp Ser Pro Ala Gly Lys Asn Gly Thr Leu Lys Pro Gly Asp
225 230 235

aga atc gta gag gtg gat gga atg gac ctc aga gat gca agc cat gaa 767
Arg Ile Val Glu Val Asp Gly Met Asp Leu Arg Asp Ala Ser His Glu
240 245 250 255

caa gct gtg gaa gcc att cgg aaa gca ggc aac cct gta gtc ttt atg 815
Gln Ala Val Glu Ala Ile Arg Lys Ala Gly Asn Pro Val Val Phe Met
260 265 270

gta tag agc ttt att aca gac caa ggg cac cca gtc agt cag agt cag 863
Val
275 280 285

ag 865

<210> 81

<211> 965

<212> DNA

<213> Homo sapience

<400> 81

tt cct tct gtg cta ccc gat tca gct gga aag ggc tct gag tac ctg 47

Pro Ser Val Leu Pro Asp Ser Ala Gly Lys Gly Ser Glu Tyr Leu

1 5 10 15

ctt gaa cag agc tcc ctg gcc tgt aat gct gag tgt gtc atg ctt caa 95

Leu Glu Gln Ser Ser Leu Ala Cys Asn Ala Glu Cys Val Met Leu Gln

20 25 30

aat gta tct aaa gaa tct ttt gaa agg act att aat ata gca aaa ggc 143

Asn Val Ser Lys Glu Ser Phe Glu Arg Thr Ile Asn Ile Ala Lys Gly

35 40 45

aat tct agc cta gga atg aca gtt agt gct aat aaa gat ggc ttg ggg 191

Asn Ser Ser Leu Gly Met Thr Val Ser Ala Asn Lys Asp Gly Leu Gly

50 55 60

atg atc gtt cga agc att att cat gga ggt gcc att agt cga gat ggc 239

Met Ile Val Arg Ser Ile Ile His Gly Gly Ala Ile Ser Arg Asp Gly

65 70 75

cgg att gcc att ggg gac tgc atc ttg tcc att aat gaa gag tct acc 287

Arg Ile Ala Ile Gly Asp Cys Ile Leu Ser Ile Asn Glu Glu Ser Thr

80 85 90 95

atc agt gta acc aat gcc cag gca cga gct atg ttg aga aga cat tct 335

Ile Ser Val Thr Asn Ala Gln Ala Arg Ala Met Leu Arg Arg His Ser

100 105 110

ctc att ggc cct gac ata aaa att act tat gtg cct gca gaa cat ttg 383

Leu Ile Gly Pro Asp Ile Lys Ile Thr Tyr Val Pro Ala Glu His Leu

115 120 125

gaa gag ttc aaa ata agc ttg gga caa caa tct gga aga gta atg gca 431

Glu Glu Phe Lys Ile Ser Leu Gly Gln Gln Ser Gly Arg Val Met Ala

130 135 140

ctg gat att ttt tct tca tac act ggc aga gac att cca gaa tta cca 479

Leu Asp Ile Phe Ser Ser Tyr Thr Gly Arg Asp Ile Pro Glu Leu Pro

145 150 155

gag cga gaa gag gga gag ggt gaa gaa agc gaa ctt caa aac aca gca 527

Glu Arg Glu Glu Gly Glu Gly Glu Glu Ser Glu Leu Gln Asn Thr Ala

160 165 170 175

tat agc aat tgg aat cag ccc agg cgg gtg gaa ctc tgg aga gaa cca 575

Tyr Ser Asn Trp Asn Gln Pro Arg Arg Val Glu Leu Trp Arg Glu Pro

180 185 190

agc aaa tcc tta ggc atc agc att gtt ggt gga cga ggg atg ggg agt 623

Ser Lys Ser Leu Gly Ile Ser Ile Val Gly Gly Arg Gly Met Gly Ser

195 200 205

cgg cta agc aat gga gaa gtg atg agg ggc att ttc atc aaa cat gtt 671

Arg Leu Ser Asn Gly Glu Val Met Arg Gly Ile Phe Ile Lys His Val

210 215 220

ctg gaa gat agt cca gct ggc aaa aat gga acc ttg aaa cct gga gat 719
Leu Glu Asp Ser Pro Ala Gly Lys Asn Gly Thr Leu Lys Pro Gly Asp
225 230 235

aga atc gta gag gtg gat gga atg gac ctc aga gat gca agc cat gaa 767
Arg Ile Val Glu Val Asp Gly Met Asp Leu Arg Asp Ala Ser His Glu
240 245 250 255

caa gct gtg gaa gcc att cgg aaa gca ggc aac cct gta gtc ttt atg 815
Gln Ala Val Glu Ala Ile Arg Lys Ala Gly Asn Pro Val Val Phe Met
260 265 270

gta cag agc att ata aac aga cca agg aaa tcc cct ttg cct tcc ttg 863
Val Gln Ser Ile Ile Asn Arg Pro Arg Lys Ser Pro Leu Pro Ser Leu
275 280 285

ctg cac aac ctt tac cct aag tac aac ttc agc agc act aac cca ttt 911
Leu His Asn Leu Tyr Pro Lys Tyr Asn Phe Ser Ser Thr Asn Pro Phe
290 295 300

gct gac tct cta caa atc aac gcc gac aag gca ccc agt cag tca gag 959
Ala Asp Ser Leu Gln Ile Asn Ala Asp Lys Ala Pro Ser Gln Ser Glu
305 310 315

tca gag 965
Ser Glu

320

<210> 82

<211> 2000

<212> PRT

<213> Homo sapience

<400> 82

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            1               5                  10
Ala Glu Arg Leu Gln Thr Lys Leu Arg Glu Arg Gly Asp Val Ala Asn
     15                  20                  25
Glu Asp Lys Leu Ser Leu Leu Lys Ser Val Leu Gln Ser Pro Leu Phe
 30                  35                  40                  45
Ser Gln Ile Leu Ser Leu Gln Thr Ser Val Gln Gln Leu Lys Asp Gln
                 50                  55                  60
Val Asn Ile Ala Thr Ser Ala Thr Ser Asn Ile Glu Tyr Ala His Val
             65                  70                  75
Pro His Leu Ser Pro Ala Val Ile Pro Thr Leu Gln Asn Glu Ser Phe
         80                  85                  90
Leu Leu Ser Pro Asn Asn Gly Asn Leu Glu Ala Leu Thr Gly Pro Gly
     95                  100                 105
Ile Pro His Ile Asn Gly Lys Pro Ala Cys Asp Glu Phe Asp Gln Leu
110                 115                 120                 125
Ile Lys Asn Met Ala Gln Gly Arg His Val Glu Val Phe Glu Leu Leu
                130                 135                 140
Lys Pro Pro Ser Gly Gly Leu Gly Phe Ser Val Val Gly Leu Arg Ser
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145 150 155

Glu Asn Arg Gly Glu Leu Gly Ile Phe Val Gln Glu Ile Gln Glu Gly

160 165 170

Ser Val Ala His Arg Asp Gly Arg Leu Lys Glu Thr Asp Gln Ile Leu

175 180 185

Ala Ile Asn Gly Gln Ala Leu Asp Gln Thr Ile Thr His Gln Gln Ala

190 195 200 205

Ile Ser Ile Leu Gln Lys Ala Lys Asp Thr Val Gln Leu Val Ile Ala

210 215 220

Arg Gly Ser Leu Pro Gln Leu Val Ser Pro Ile Val Ser Arg Ser Pro

225 230 235

Ser Ala Ala Ser Thr Ile Ser Ala His Ser Asn Pro Val His Trp Gln

240 245 250

His Met Glu Thr Ile Glu Leu Val Asn Asp Gly Ser Gly Leu Gly Phe

255 260 265

Gly Ile Ile Gly Gly Lys Ala Thr Gly Val Ile Val Lys Thr Ile Leu

270 275 280 285

Pro Gly Gly Val Ala Asp Gln His Gly Arg Leu Cys Ser Gly Asp His

290 295 300

Ile Leu Lys Ile Gly Asp Thr Asp Leu Ala Gly Met Ser Ser Glu Gln

305 310 315

Val Ala Gln Val Leu Arg Gln Cys Gly Asn Arg Val Lys Leu Met Ile

320 325 330

Ala Arg Ser Ala Ile Glu Glu Arg Thr Ala Pro Thr Ala Leu Gly Ile

335 340 345

Thr Leu Ser Ser Ser Pro Thr Ser Thr Pro Glu Leu Arg Val Asp Ala

350 355 360 365

Ser Thr Gln Lys Gly Glu Glu Ser Glu Thr Phe Asp Val Glu Leu Thr
370 375 380
Lys Asn Val Gln Gly Leu Gly Ile Thr Ile Ala Gly Tyr Ile Gly Asp
385 390 395
Lys Lys Leu Glu Pro Ser Gly Ile Phe Val Lys Ser Ile Thr Lys Ser
400 405 410
Ser Ala Val Glu His Asp Gly Arg Ile Gln Ile Gly Asp Gln Ile Ile
415 420 425
Ala Val Asp Gly Thr Asn Leu Gln Gly Phe Thr Asn Gln Gln Ala Val
430 435 440 445
Glu Val Leu Arg His Thr Gly Gln Thr Val Leu Leu Thr Leu Met Arg
450 455 460
Arg Gly Met Lys Gln Glu Ala Glu Leu Met Ser Arg Glu Asp Val Thr
465 470 475
Lys Asp Ala Asp Leu Ser Pro Val Asn Ala Ser Ile Ile Lys Glu Asn
480 485 490
Tyr Glu Lys Asp Glu Asp Phe Leu Ser Ser Thr Arg Asn Thr Asn Ile
495 500 505
Leu Pro Thr Glu Glu Glu Gly Tyr Pro Leu Leu Ser Ala Glu Ile Glu
510 515 520 525
Glu Ile Glu Asp Ala Gln Lys Gln Glu Ala Ala Leu Leu Thr Lys Trp
530 535 540
Gln Arg Ile Met Gly Ile Asn Tyr Glu Ile Val Val Ala His Val Ser
545 550 555
Lys Phe Ser Glu Asn Ser Gly Leu Gly Ile Ser Leu Glu Ala Thr Val
560 565 570
Gly His His Phe Ile Arg Ser Val Leu Pro Glu Gly Pro Val Gly His

575 580 585

Ser Gly Lys Leu Phe Ser Gly Asp Glu Leu Leu Glu Val Asn Gly Ile

590 595 600 605

Thr Leu Leu Gly Glu Asn His Gln Asp Val Val Asn Ile Leu Lys Glu

610 615 620

Leu Pro Ile Glu Val Thr Met Val Cys Cys Arg Arg Thr Val Pro Pro

625 630 635

Thr Thr Gln Ser Glu Leu Asp Ser Leu Asp Leu Cys Asp Ile Glu Leu

640 645 650

Thr Glu Lys Pro His Val Asp Leu Gly Glu Phe Ile Gly Ser Ser Glu

655 660 665

Pro Glu Asp Pro Val Leu Ala Met Thr Asp Ala Gly Gln Ser Thr Glu

670 675 680 685

Glu Val Gln Ala Pro Leu Ala Met Trp Glu Ala Gly Ile Gln His Ile

690 695 700

Met Leu Glu Lys Gly Ser Lys Gly Leu Gly Phe Ser Ile Leu Asp Tyr

705 710 715

Gln Asp Pro Ile Asp Pro Ala Ser Thr Val Ile Ile Ile Arg Ser Leu

720 725 730

Val Pro Gly Gly Ile Ala Glu Lys Asp Gly Arg Leu Leu Pro Gly Asp

735 740 745

Arg Leu Met Phe Val Asn Asp Val Asn Leu Glu Asn Ser Ser Leu Glu

750 755 760 765

Glu Ala Val Glu Ala Leu Lys Gly Ala Pro Ser Gly Thr Val Arg Ile

770 775 780

Gly Val Ala Lys Pro Leu Pro Leu Ser Pro Glu Glu Gly Tyr Val Ser

785 790 795

Ala Lys Glu Asp Ser Phe Leu Tyr Pro Pro His Ser Cys Glu Glu Ala
800 805 810
Gly Leu Ala Asp Lys Pro Leu Phe Arg Ala Asp Leu Ala Leu Val Gly
815 820 825
Thr Asn Asp Ala Asp Leu Val Asp Glu Ser Thr Phe Glu Ser Pro Tyr
830 835 840 845
Ser Pro Glu Asn Asp Ser Ile Tyr Ser Thr Gln Ala Ser Ile Leu Ser
850 855 860
Leu His Gly Ser Ser Cys Gly Asp Gly Leu Asn Tyr Gly Ser Ser Leu
865 870 875
Pro Ser Ser Pro Pro Lys Asp Val Ile Glu Asn Ser Cys Asp Pro Val
880 885 890
Leu Asp Leu His Met Ser Leu Glu Glu Leu Tyr Thr Gln Asn Leu Leu
895 900 905
Glu Arg Gln Asp Glu Asn Thr Pro Ser Val Asp Ile Ser Met Gly Pro
910 915 920 925
Ala Ser Gly Phe Thr Ile Asn Asp Tyr Thr Pro Ala Asn Ala Ile Glu
930 935 940
Gln Gln Tyr Glu Cys Glu Asn Thr Ile Val Trp Thr Glu Ser His Leu
945 950 955
Pro Ser Glu Val Ile Ser Ser Ala Glu Leu Pro Ser Val Leu Pro Asp
960 965 970
Ser Ala Gly Lys Gly Ser Glu His Leu Leu Glu Gln Ser Ser Leu Ala
975 980 985
Cys Asn Ala Glu Cys Val Met Leu Gln Asn Val Ser Lys Glu Ser Phe
990 995 1000 1005
Glu Arg Thr Ile Asn Ile Ala Lys Gly Asn Ser Ser Leu Gly Met Thr

1010 1015 1020

Val Ser Ala Asn Lys Asp Gly Leu Gly Met Ile Val Arg Ser Ile Ile

1025 1030 1035

His Gly Gly Ala Ile Ser Arg Asp Gly Arg Ile Ala Ile Gly Asp Cys

1040 1045 1050

Ile Leu Ser Ile Asn Glu Glu Ser Thr Ile Ser Val Thr Asn Ala Gln

1055 1060 1065

Ala Arg Ala Met Leu Arg Arg His Ser Leu Ile Gly Pro Asp Ile Lys

1070 1075 1080 1085

Ile Thr Tyr Val Pro Ala Glu His Leu Glu Glu Phe Lys Ile Ser Leu

1090 1095 1100

Gly Gln Gln Ser Gly Arg Val Met Ala Leu Asp Ile Phe Ser Ser Tyr

1105 1110 1115

Thr Gly Arg Asp Ile Pro Glu Leu Pro Glu Arg Glu Glu Gly Glu Gly

1120 1125 1130

Glu Glu Ser Glu Leu Gln Asn Thr Ala Tyr Ser Asn Trp Asn Gln Pro

1135 1140 1145

Arg Arg Val Glu Leu Trp Arg Glu Pro Ser Lys Ser Leu Gly Ile Ser

1150 1155 1160 1165

Ile Val Gly Gly Arg Gly Met Gly Ser Arg Leu Ser Asn Gly Glu Val

1170 1175 1180

Met Arg Gly Ile Phe Ile Lys His Val Leu Glu Asp Ser Pro Ala Gly

1185 1190 1195

Lys Asn Gly Thr Leu Lys Pro Gly Asp Arg Ile Val Glu Ala Pro Ser

1200 1205 1210

Gln Ser Glu Ser Glu Pro Glu Lys Ala Pro Leu Cys Ser Val Pro Pro

1215 1220 1225

Pro Pro Pro Ser Ala Phe Ala Glu Met Gly Ser Asp His Thr Gln Ser
1230 1235 1240 1245
Ser Ala Ser Lys Ile Ser Gln Asp Val Asp Lys Glu Asp Glu Phe Gly
1250 1255 1260
Tyr Ser Trp Lys Asn Ile Arg Glu Arg Tyr Gly Thr Leu Thr Gly Glu
1265 1270 1275
Leu His Met Ile Glu Leu Glu Lys Gly His Ser Gly Leu Gly Leu Ser
1280 1285 1290
Leu Ala Gly Asn Lys Asp Arg Ser Arg Met Ser Val Phe Ile Val Gly
1295 1300 1305
Ile Asp Pro Asn Gly Ala Ala Gly Lys Asp Gly Arg Leu Gln Ile Ala
1310 1315 1320 1325
Asp Glu Leu Leu Glu Ile Asn Gly Gln Ile Leu Tyr Gly Arg Ser His
1330 1335 1340
Gln Asn Ala Ser Ser Ile Ile Lys Cys Ala Pro Ser Lys Val Lys Ile
1345 1350 1355
Ile Phe Ile Arg Asn Lys Asp Ala Val Asn Gln Met Ala Val Cys Pro
1360 1365 1370
Gly Asn Ala Val Glu Pro Leu Pro Ser Asn Ser Glu Asn Leu Gln Asn
1375 1380 1385
Lys Glu Thr Glu Pro Thr Val Thr Thr Ser Asp Ala Ala Val Asp Leu
1390 1395 1400 1405
Ser Ser Phe Lys Asn Val Gln His Leu Glu Leu Pro Lys Asp Gln Gly
1410 1415 1420
Gly Leu Gly Ile Ala Ile Ser Glu Glu Asp Thr Leu Ser Gly Val Ile
1425 1430 1435
Ile Lys Ser Leu Thr Glu His Gly Val Ala Ala Thr Asp Gly Arg Leu

1440 1445 1450

Lys Val Gly Asp Gln Ile Leu Ala Val Asp Asp Glu Ile Val Val Gly

1455 1460 1465

Tyr Pro Ile Glu Lys Phe Ile Ser Leu Leu Lys Thr Ala Lys Met Thr

1470 1475 1480 1485

Val Lys Leu Thr Ile His Ala Glu Asn Pro Asp Ser Gln Ala Val Pro

1490 1495 1500

Ser Ala Ala Gly Ala Ala Ser Gly Glu Lys Lys Asn Ser Ser Gln Ser

1505 1510 1515

Leu Met Val Pro Gln Ser Gly Ser Pro Glu Pro Glu Ser Ile Arg Asn

1520 1525 1530

Thr Ser Arg Ser Ser Thr Pro Ala Ile Phe Ala Ser Asp Pro Ala Thr

1535 1540 1545

Cys Pro Ile Ile Pro Gly Cys Glu Thr Thr Ile Glu Ile Ser Lys Gly

1550 1555 1560 1565

Arg Thr Gly Leu Gly Leu Ser Ile Val Gly Gly Ser Asp Thr Leu Leu

1570 1575 1580

Gly Ala Phe Ile Ile His Glu Val Tyr Glu Glu Gly Ala Ala Cys Lys

1585 1590 1595

Asp Gly Arg Leu Trp Ala Gly Asp Gln Ile Leu Glu Val Asn Gly Ile

1600 1605 1610

Asp Leu Arg Lys Ala Thr His Asp Glu Ala Ile Asn Val Leu Arg Gln

1615 1620 1625

Thr Pro Gln Arg Val Arg Leu Thr Leu Tyr Arg Asp Glu Ala Pro Tyr

1630 1635 1640 1645

Lys Glu Glu Glu Val Cys Asp Thr Leu Thr Ile Glu Leu Gln Lys Lys

1650 1655 1660

Pro Gly Lys Gly Leu Gly Leu Ser Ile Val Gly Lys Arg Asn Asp Thr

1665 1670 1675

Gly Val Phe Val Ser Asp Ile Val Lys Gly Gly Ile Ala Asp Pro Asp

1680 1685 1690

Gly Arg Leu Ile Gln Gly Asp Gln Ile Leu Leu Val Asn Gly Glu Asp

1695 1700 1705

Val Arg Asn Ala Ser Gln Glu Ala Val Ala Ala Leu Leu Lys Cys Ser

1710 1715 1720 1725

Leu Gly Thr Val Thr Leu Glu Val Gly Arg Ile Lys Ala Gly Pro Phe

1730 1735 1740

His Ser Glu Arg Arg Pro Ser Gln Thr Ser Gln Val Ser Glu Gly Ser

1745 1750 1755

Leu Ser Ser Phe Thr Phe Pro Leu Ser Gly Ser Ser Thr Ser Glu Ser

1760 1765 1770

Leu Glu Ser Ser Ser Lys Lys Asn Ala Leu Ala Ser Glu Ile Gln Gly

1775 1780 1785

Leu Arg Thr Val Glu Met Lys Lys Gly Pro Thr Asp Ser Leu Gly Ile

1790 1795 1800 1805

Ser Ile Ala Gly Gly Val Gly Ser Pro Leu Gly Asp Val Pro Ile Phe

1810 1815 1820

Ile Ala Met Met His Pro Thr Gly Val Ala Ala Gln Thr Gln Lys Leu

1825 1830 1835

Arg Val Gly Asp Arg Ile Val Thr Ile Cys Gly Thr Ser Thr Glu Gly

1840 1845 1850

Met Thr His Thr Gln Ala Val Asn Leu Leu Lys Asn Ala Ser Gly Ser

1855 1860 1865

Ile Glu Met Gln Val Val Ala Gly Gly Asp Val Ser Val Val Thr Gly

1870 1875 1880 1885

His His Gln Glu Pro Ala Ser Ser Ser Leu Ser Phe Thr Gly Leu Thr

1890 1895 1900

Ser Thr Ser Ile Phe Gln Asp Asp Leu Gly Pro Pro Gln Cys Lys Ser

1905 1910 1915

Ile Thr Leu Glu Arg Gly Pro Asp Gly Leu Gly Phe Ser Ile Val Gly

1920 1925 1930

Gly Tyr Gly Ser Pro His Gly Asp Leu Pro Ile Tyr Val Lys Thr Val

1935 1940 1945

Phe Ala Lys Gly Ala Ala Ser Glu Asp Gly Arg Leu Lys Arg Gly Asp

1950 1955 1960 1965

Gln Ile Ile Ala Val Asn Gly Gln Ser Leu Glu Gly Val Thr His Glu

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Glu Ala Val Ala Ile Leu Lys Arg Thr Lys Gly Thr Val Thr Leu Met

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 30                  35                  40                  45
Ser Gln Ile Leu Ser Leu Gln Thr Ser Val Gln Gln Leu Lys Asp Gln
                 50                  55                  60
Val Asn Ile Ala Thr Ser Ala Thr Ser Asn Ile Glu Tyr Ala His Val
             65                  70                  75
Pro His Leu Ser Pro Ala Val Ile Pro Thr Leu Gln Asn Glu Ser Phe
         80                  85                  90
Leu Leu Ser Pro Asn Asn Gly Asn Leu Glu Ala Leu Thr Gly Pro Gly
     95                 100                 105
Ile Pro His Ile Asn Gly Lys Pro Ala Cys Asp Glu Phe Asp Gln Leu
110                 115                 120                 125
Ile Lys Asn Met Ala Gln Gly Arg His Val Glu Val Phe Glu Leu Leu
                130                 135                 140
Lys Pro Pro Ser Gly Gly Leu Gly Phe Ser Val Val Gly Leu Arg Ser
            145                 150                 155
Glu Asn Arg Gly Glu Leu Gly Ile Phe Val Gln Glu Ile Gln Glu Gly
        160                 165                 170
Ser Val Ala His Arg Asp Gly Arg Leu Lys Glu Thr Asp Gln Ile Leu
    175                 180                 185
Ala Ile Asn Gly Gln Ala Leu Asp Gln Thr Ile Thr His Gln Gln Ala
190                 195                 200                 205
Ile Ser Ile Leu Gln Lys Ala Lys Asp Thr Val Gln Leu Val Ile Ala
                210                 215                 220
Arg Gly Ser Leu Pro Gln Leu Val Ser Pro Ile Val Ser Arg Ser Pro
            225                 230                 235
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Ser Ala Ala Ser Thr Ile Ser Ala His Ser Asn Pro Val His Trp Gln

240 245 250

His Met Glu Thr Ile Glu Leu Val Asn Asp Gly Ser Gly Leu Gly Phe

255 260 265

Gly Ile Ile Gly Gly Lys Ala Thr Gly Val Ile Val Lys Thr Ile Leu

270 275 280 285

Pro Gly Gly Val Ala Asp Gln His Gly Arg Leu Cys Ser Gly Asp His

290 295 300

Ile Leu Lys Ile Gly Asp Thr Asp Leu Ala Gly Met Ser Ser Glu Gln

305 310 315

Val Ala Gln Val Leu Arg Gln Cys Gly Asn Arg Val Lys Leu Met Ile

320 325 330

Ala Arg Ser Ala Ile Glu Glu Arg Thr Ala Pro Thr Ala Leu Gly Ile

335 340 345

Thr Leu Ser Ser Ser Pro Thr Ser Thr Pro Glu Leu Arg Val Asp Ala

350 355 360 365

Ser Thr Gln Lys Gly Glu Glu Ser Glu Thr Phe Asp Val Glu Leu Thr

370 375 380

Lys Asn Val Gln Gly Leu Gly Ile Thr Ile Ala Gly Tyr Ile Gly Asp

385 390 395

Lys Lys Leu Glu Pro Ser Gly Ile Phe Val Lys Ser Ile Thr Lys Ser

400 405 410

Ser Ala Val Glu His Asp Gly Arg Ile Gln Ile Gly Asp Gln Ile Ile

415 420 425

Ala Val Asp Gly Thr Asn Leu Gln Gly Phe Thr Asn Gln Gln Ala Val

430 435 440 445

Glu Val Leu Arg His Thr Gly Gln Thr Val Leu Leu Thr Leu Met Arg

450 455 460

Arg Gly Met Lys Gln Glu Ala Glu Leu Met Ser Arg Glu Asp Val Thr

465 470 475

Lys Asp Ala Asp Leu Ser Pro Val Asn Ala Ser Ile Ile Lys Glu Asn

480 485 490

Tyr Glu Lys Asp Glu Asp Phe Leu Ser Ser Thr Arg Asn Thr Asn Ile

495 500 505

Leu Pro Thr Glu Glu Glu Gly Tyr Pro Leu Leu Ser Ala Glu Ile Glu

510 515 520 525

Glu Ile Glu Asp Ala Gln Lys Gln Glu Ala Ala Leu Leu Thr Lys Trp

530 535 540

Gln Arg Ile Met Gly Ile Asn Tyr Glu Ile Val Val Ala His Val Ser

545 550 555

Lys Phe Ser Glu Asn Ser Gly Leu Gly Ile Ser Leu Glu Ala Thr Val

560 565 570

Gly His His Phe Ile Arg Ser Val Leu Pro Glu Gly Pro Val Gly His

575 580 585

Ser Gly Lys Leu Phe Ser Gly Asp Glu Leu Leu Glu Val Asn Gly Ile

590 595 600 605

Thr Leu Leu Gly Glu Asn His Gln Asp Val Val Asn Ile Leu Lys Glu

610 615 620

Leu Pro Ile Glu Val Thr Met Val Cys Cys Arg Arg Thr Val Pro Pro

625 630 635

Thr Thr Gln Ser Glu Leu Asp Ser Leu Asp Leu Cys Asp Ile Glu Leu

640 645 650

Thr Glu Lys Pro His Val Asp Leu Gly Glu Phe Ile Gly Ser Ser Glu

655 660 665

Pro Glu Asp Pro Val Leu Ala Met Thr Asp Ala Gly Gln Ser Thr Glu
670 675 680 685
Glu Val Gln Ala Pro Leu Ala Met Trp Glu Ala Gly Ile Gln His Ile
690 695 700
Met Leu Glu Lys Gly Ser Lys Gly Leu Gly Phe Ser Ile Leu Asp Tyr
705 710 715
Gln Asp Pro Ile Asp Pro Ala Ser Thr Val Ile Ile Ile Arg Ser Leu
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Val Pro Gly Gly Ile Ala Glu Lys Asp Gly Arg Leu Leu Pro Gly Asp
735 740 745
Arg Leu Met Phe Val Asn Asp Val Asn Leu Glu Asn Ser Ser Leu Glu
750 755 760 765
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770 775 780
Gly Val Ala Lys Pro Leu Pro Leu Ser Pro Glu Glu Gly Tyr Val Ser
785 790 795
Ala Lys Glu Asp Ser Phe Leu Tyr Pro Pro His Ser Cys Glu Glu Ala
800 805 810
Gly Leu Ala Asp Lys Pro Leu Phe Arg Ala Asp Leu Ala Leu Val Gly
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Thr Asn Asp Ala Asp Leu Val Asp Glu Ser Thr Phe Glu Ser Pro Tyr
830 835 840 845
Ser Pro Glu Asn Asp Ser Ile Tyr Ser Thr Gln Ala Ser Ile Leu Ser
850 855 860
Leu His Gly Ser Ser Cys Gly Asp Gly Leu Asn Tyr Gly Ser Ser Leu
865 870 875
Pro Ser Ser Pro Pro Lys Asp Val Ile Glu Asn Ser Cys Asp Pro Val

880 885 890

Leu Asp Leu His Met Ser Leu Glu Glu Leu Tyr Thr Gln Asn Leu Leu

895 900 905

Glu Arg Gln Asp Glu Asn Thr Pro Ser Val Asp Ile Ser Met Gly Pro

910 915 920 925

Ala Ser Gly Phe Thr Ile Asn Asp Tyr Thr Pro Ala Asn Ala Ile Glu

930 935 940

Gln Gln Tyr Glu Cys Glu Asn Thr Ile Val Trp Thr Glu Ser His Leu

945 950 955

Pro Ser Glu Val Ile Ser Ser Ala Glu Leu Pro Ser Val Leu Pro Asp

960 965 970

Ser Ala Gly Lys Gly Ser Glu Tyr Leu Leu Glu Gln Ser Ser Leu Ala

975 980 985

Cys Asn Ala Glu Cys Val Met Leu Gln Asn Val Ser Lys Glu Ser Phe

990 995 1000 1005

Glu Arg Thr Ile Asn Ile Ala Lys Gly Asn Ser Ser Leu Gly Met Thr

1010 1015 1020

Val Ser Ala Asn Lys Asp Gly Leu Gly Met Ile Val Arg Ser Ile Ile

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His Gly Gly Ala Ile Ser Arg Asp Gly Arg Ile Ala Ile Gly Asp Cys

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Ile Leu Ser Ile Asn Glu Glu Ser Thr Ile Ser Val Thr Asn Ala Gln

1055 1060 1065

Ala Arg Ala Met Leu Arg Arg His Ser Leu Ile Gly Pro Asp Ile Lys

1070 1075 1080 1085

Ile Thr Tyr Val Pro Ala Glu His Leu Glu Glu Phe Lys Ile Ser Leu

1090 1095 1100

Gly Gln Gln Ser Gly Arg Val Met Ala Leu Asp Ile Phe Ser Ser Tyr
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Arg Arg Val Glu Leu Trp Arg Glu Pro Ser Lys Ser Leu Gly Ile Ser
1150 1155 1160 1165

Ile Val Gly Gly Arg Gly Met Gly Ser Arg Leu Ser Asn Gly Glu Val
1170 1175 1180

Met Arg Gly Ile Phe Ile Lys His Val Leu Glu Asp Arg Pro Ala Gly
1185 1190 1195

Lys Asn Gly Thr Leu Lys Pro Gly Asp Arg Ile Val Glu Val Asp Gly
1200 1205 1210

Met Asp Leu Arg Asp Ala Ser His Glu Gln Ala Val Glu Ala Ile Arg
1215 1220 1225

Lys Ala Gly Asn Pro Val Val Phe Met Val Gln Ser Ile Ile Asn Arg
1230 1235 1240 1245

Pro Arg Lys Ser Pro Leu Pro Ser Leu Leu His Asn Leu Tyr Pro Lys
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Tyr Asn Phe Ser Ser Thr Asn Pro Phe Ala Asp Ser Leu Gln Ile Asn
1265 1270 1275

Ala Asp Lys Ala Pro Ser Gln Ser Glu Ser Glu Pro Glu Lys Ala Pro
1280 1285 1290

Leu Cys Ser Val Pro Pro Pro Pro Pro Ser Ala Phe Ala Glu Met Gly
1295 1300 1305

Ser Asp His Thr Gln Ser Ser Ala Ser Lys Ile Ser Gln Asp Val Asp

1310 1315 1320 1325

Lys Glu Asp Glu Phe Gly Tyr Ser Trp Lys Asn Ile Arg Glu Arg Tyr

1330 1335 1340

Gly Thr Leu Thr Gly Glu Leu His Met Ile Glu Leu Glu Lys Gly His

1345 1350 1355

Ser Gly Leu Gly Leu Ser Leu Ala Gly Asn Lys Asp Arg Ser Arg Met

1360 1365 1370

Ser Val Phe Ile Val Gly Ile Asp Pro Asn Gly Ala Ala Gly Lys Asp

1375 1380 1385

Gly Arg Leu Gln Ile Ala Asp Glu Leu Leu Glu Ile Asn Gly Gln Ile

1390 1395 1400 1405

Leu Tyr Gly Arg Ser His Gln Asn Ala Ser Ser Ile Ile Lys Cys Ala

1410 1415 1420

Pro Ser Lys Val Lys Ile Ile Phe Ile Arg Asn Lys Asp Ala Val Asn

1425 1430 1435

Gln Met Ala Val Cys Pro Gly Asn Ala Val Glu Pro Leu Pro Ser Asn

1440 1445 1450

Ser Glu Asn Leu Gln Asn Lys Glu Thr Glu Pro Thr Val Thr Thr Ser

1455 1460 1465

Asp Ala Ala Val Asp Leu Ser Ser Phe Lys Asn Val Gln His Leu Glu

1470 1475 1480 1485

Leu Pro Lys Asp Gln Gly Gly Leu Gly Ile Ala Ile Ser Glu Glu Asp

1490 1495 1500

Thr Leu Ser Gly Val Ile Ile Lys Ser Leu Thr Glu His Gly Val Ala

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Ala Thr Asp Gly Arg Leu Lys Val Gly Asp Gln Ile Leu Ala Val Asp

1520 1525 1530

Asp Glu Ile Val Val Gly Tyr Pro Ile Glu Lys Phe Ile Ser Leu Leu
1535 1540 1545

Lys Thr Ala Lys Met Thr Val Lys Leu Thr Ile His Ala Glu Asn Pro
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Asp Ser Gln Ala Val Pro Ser Ala Ala Gly Ala Ala Ser Gly Glu Lys
1570 1575 1580

Lys Asn Ser Ser Gln Ser Leu Met Val Pro Gln Ser Gly Ser Pro Glu
1585 1590 1595

Pro Glu Ser Ile Arg Asn Thr Ser Arg Ser Ser Thr Pro Ala Ile Phe
1600 1605 1610

Ala Ser Asp Pro Ala Thr Cys Pro Ile Ile Pro Gly Cys Glu Thr Thr
1615 1620 1625

Ile Glu Ile Ser Lys Gly Arg Thr Gly Leu Gly Leu Ser Ile Val Gly
1630 1635 1640 1645

Gly Ser Asp Thr Leu Leu Gly Ala Phe Ile Ile His Glu Val Tyr Glu
1650 1655 1660

Glu Gly Ala Ala Cys Lys Asp Gly Arg Leu Trp Ala Gly Asp Gln Ile
1665 1670 1675

Leu Glu Val Asn Gly Ile Asp Leu Arg Lys Ala Thr His Asp Glu Ala
1680 1685 1690

Ile Asn Val Leu Arg Gln Thr Pro Gln Arg Val Arg Leu Thr Leu Tyr
1695 1700 1705

Arg Asp Glu Ala Pro Tyr Lys Glu Glu Glu Val Cys Asp Thr Leu Thr
1710 1715 1720 1725

Ile Glu Leu Gln Lys Lys Pro Gly Lys Gly Leu Gly Leu Ser Ile Val
1730 1735 1740

Gly Lys Arg Asn Asp Thr Gly Val Phe Val Ser Asp Ile Val Lys Gly

1745 1750 1755

Gly Ile Ala Asp Pro Asp Gly Arg Leu Ile Gln Gly Asp Gln Ile Leu

1760 1765 1770

Leu Val Asn Gly Glu Asp Val Arg Asn Ala Ser Gln Glu Ala Val Ala

1775 1780 1785

Ala Leu Leu Lys Cys Ser Leu Gly Thr Val Thr Leu Glu Val Gly Arg

1790 1795 1800 1805

Ile Lys Ala Gly Pro Phe His Ser Glu Arg Arg Pro Ser Gln Thr Ser

1810 1815 1820

Gln Val Ser Glu Gly Ser Leu Ser Ser Phe Thr Phe Pro Leu Ser Gly

1825 1830 1835

Ser Ser Thr Ser Glu Ser Leu Glu Ser Ser Ser Lys Lys Asn Ala Leu

1840 1845 1850

Ala Ser Glu Ile Gln Gly Leu Arg Thr Val Glu Met Lys Lys Gly Pro

1855 1860 1865

Thr Asp Ser Leu Gly Ile Ser Ile Ala Gly Gly Val Gly Ser Pro Leu

1870 1875 1880 1885

Gly Asp Val Pro Ile Phe Ile Ala Met Met His Pro Thr Gly Val Ala

1890 1895 1900

Ala Gln Thr Gln Lys Leu Arg Val Gly Asp Arg Ile Val Thr Ile Cys

1905 1910 1915

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1920 1925 1930

Lys Asn Ala Ser Gly Ser Ile Glu Met Gln Val Val Ala Gly Gly Asp

1935 1940 1945

Val Ser Val Val Thr Gly His His Gln Glu Pro Ala Ser Ser Ser Leu

1950 1955 1960 1965

Ser Phe Thr Gly Leu Thr Ser Thr Ser Ile Phe Gln Asp Asp Leu Gly
1970 1975 1980
Pro Pro Gln Cys Lys Ser Ile Thr Leu Glu Arg Gly Pro Asp Gly Leu
1985 1990 1995
Gly Phe Ser Ile Val Gly Gly Tyr Gly Ser Pro His Gly Asp Leu Pro
2000 2005 2010
Ile Tyr Val Lys Thr Val Phe Ala Lys Gly Ala Ala Ser Glu Asp Gly
2015 2020 2025
Arg Leu Lys Arg Gly Asp Gln Ile Ile Ala Val Asn Gly Gln Ser Leu
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30 35 40 45

Ser Gln Ile Leu Ser Leu Gln Thr Ser Val Gln Gln Leu Lys Asp Gln

50 55 60

Val Asn Ile Ala Thr Ser Ala Thr Ser Asn Ile Glu Tyr Ala His Val

65 70 75

Pro His Leu Ser Pro Ala Val Ile Pro Thr Leu Gln Asn Glu Ser Phe

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Leu Leu Ser Pro Asn Asn Gly Asn Leu Glu Ala Leu Thr Gly Pro Gly

95 100 105

Ile Pro His Ile Asn Gly Lys Pro Ala Cys Asp Glu Phe Asp Gln Leu

110 115 120 125

Ile Lys Asn Met Ala Gln Gly Arg His Val Glu Val Phe Glu Leu Leu

130 135 140

Lys Pro Pro Ser Gly Gly Leu Gly Phe Ser Val Val Gly Leu Arg Ser

145 150 155

Glu Asn Arg Gly Glu Leu Gly Ile Phe Val Gln Glu Ile Gln Glu Gly

160 165 170

Ser Val Ala His Arg Asp Gly Arg Leu Lys Glu Thr Asp Gln Ile Leu

175 180 185

Ala Ile Asn Gly Gln Ala Leu Asp Gln Thr Ile Thr His Gln Gln Ala

190 195 200 205

Ile Ser Ile Leu Gln Lys Ala Lys Asp Thr Val Gln Leu Val Ile Ala

210 215 220

Arg Gly Ser Leu Pro Gln Leu Val Ser Pro Ile Val Ser Arg Ser Pro

225 230 235

Ser Ala Ala Ser Thr Ile Ser Ala His Ser Asn Pro Val His Trp Gln

240 245 250

His Met Glu Thr Ile Glu Leu Val Asn Asp Gly Ser Gly Leu Gly Phe

255 260 265

Gly Ile Ile Gly Gly Lys Ala Thr Gly Val Ile Val Lys Thr Ile Leu

270 275 280 285

Pro Gly Gly Val Ala Asp Gln His Gly Arg Leu Cys Ser Gly Asp His

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Ile Leu Lys Ile Gly Asp Thr Asp Leu Ala Gly Met Ser Ser Glu Gln

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Val Ala Gln Val Leu Arg Gln Cys Gly Asn Arg Val Lys Leu Met Ile

320 325 330

Ala Arg Ser Ala Ile Glu Glu Arg Thr Ala Pro Thr Ala Leu Gly Ile

335 340 345

Thr Leu Ser Ser Ser Pro Thr Ser Thr Pro Glu Leu Arg Val Asp Ala

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Ser Thr Gln Lys Gly Glu Glu Ser Glu Thr Phe Asp Val Glu Leu Thr

370 375 380

Lys Asn Val Gln Gly Leu Gly Ile Thr Ile Ala Gly Tyr Ile Gly Asp

385 390 395

Lys Lys Leu Glu Pro Ser Gly Ile Phe Val Lys Ser Ile Thr Lys Ser

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Ser Ala Val Glu His Asp Gly Arg Ile Gln Ile Gly Asp Gln Ile Ile

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450 455 460

Arg Gly Met Lys Gln Glu Ala Glu Leu Met Ser Arg Glu Asp Val Thr

465 470 475

Lys Asp Ala Asp Leu Ser Pro Val Asn Ala Ser Ile Ile Lys Glu Asn
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Tyr Glu Lys Asp Glu Asp Phe Leu Ser Ser Thr Arg Asn Thr Asn Ile
495 500 505
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Ser Gly Lys Leu Phe Ser Gly Asp Glu Leu Leu Glu Val Asn Gly Ile
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Thr Leu Leu Gly Glu Asn His Gln Asp Val Val Asn Ile Leu Lys Glu
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Thr Glu Lys Pro His Val Asp Leu Gly Glu Phe Ile Gly Ser Ser Glu
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Pro Glu Asp Pro Val Leu Ala Met Thr Asp Ala Gly Gln Ser Thr Glu
670 675 680 685
Glu Val Gln Ala Pro Leu Ala Met Trp Glu Ala Gly Ile Gln His Ile

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Met Leu Glu Lys Gly Ser Lys Gly Leu Gly Phe Ser Ile Leu Asp Tyr

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Gln Asp Pro Ile Asp Pro Ala Ser Thr Val Ile Ile Ile Arg Ser Leu

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Val Pro Gly Gly Ile Ala Glu Lys Asp Gly Arg Leu Leu Pro Gly Asp

735 740 745

Arg Leu Met Phe Val Asn Asp Val Asn Leu Glu Asn Ser Ser Leu Glu

750 755 760 765

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770 775 780

Gly Val Ala Lys Pro Leu Pro Leu Ser Pro Glu Glu Gly Tyr Val Ser

785 790 795

Ala Lys Glu Asp Ser Phe Leu Tyr Pro Pro His Ser Cys Glu Glu Ala

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830 835 840 845

Ser Pro Glu Asn Asp Ser Ile Tyr Ser Thr Gln Ala Ser Ile Leu Ser

850 855 860

Leu His Gly Ser Ser Cys Gly Asp Gly Leu Asn Tyr Gly Ser Ser Leu

865 870 875

Pro Ser Ser Pro Pro Lys Asp Val Ile Glu Asn Ser Cys Asp Pro Val

880 885 890

Leu Asp Leu His Met Ser Leu Glu Glu Leu Tyr Thr Gln Asn Leu Leu

895 900 905

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Pro Ser Glu Val Ile Ser Ser Ala Glu Leu Pro Ser Val Leu Pro Asp
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Ser Ala Gly Lys Gly Ser Glu His Leu Leu Glu Gln Ser Ser Leu Ala
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Cys Asn Ala Glu Cys Val Met Leu Gln Asn Val Ser Lys Glu Ser Phe
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Arg Arg Val Glu Leu Trp Arg Glu Pro Ser Lys Ser Leu Gly Ile Ser

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1170 1175 1180

Met Arg Gly Ile Phe Ile Lys His Val Leu Glu Asp Ser Pro Ala Gly

1185 1190 1195

Lys Asn Gly Thr Leu Lys Pro Gly Asp Arg Ile Val Glu Val Asp Gly

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Ala Glu Arg Leu Gln Thr Lys Leu Arg Glu Arg Gly Asp Val Ala Asn
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Glu Asp Lys Leu Ser Leu Leu Lys Ser Val Leu Gln Ser Pro Leu Phe
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Ser Gln Ile Leu Ser Leu Gln Thr Ser Val Gln Gln Leu Lys Asp Gln
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Val Asn Ile Ala Thr Ser Ala Thr Ser Asn Ile Glu Tyr Ala His Val
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cct cat ctc agc cca gct gtg att cct act ctg caa aat gaa tcg ttt 349
Pro His Leu Ser Pro Ala Val Ile Pro Thr Leu Gln Asn Glu Ser Phe
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Leu Leu Ser Pro Asn Asn Gly Asn Leu Glu Ala Leu Thr Gly Pro Gly

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Ile Pro His Ile Asn Gly Lys Pro Ala Cys Asp Glu Phe Asp Gln Leu
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Ile Lys Asn Met Ala Gln Gly Arg His Val Glu Val Phe Glu Leu Leu
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Lys Pro Pro Ser Gly Gly Leu Gly Phe Ser Val Val Gly Leu Arg Ser
145 150 155

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Ser Val Ala His Arg Asp Gly Arg Leu Lys Glu Thr Asp Gln Ile Leu
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gct atc aat gga cag gct ctt gat cag aca att aca cat cag cag gct 685
Ala Ile Asn Gly Gln Ala Leu Asp Gln Thr Ile Thr His Gln Gln Ala
190 195 200 205

atc agc atc ctg cag aaa gcc aaa gat act gtc cag cta gtt att gcc 733

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Arg Gly Ser Leu Pro Gln Leu Val Ser Pro Ile Val Ser Arg Ser Pro
225 230 235

tct gca gcc agc aca att tca gct cac tct aat ccg gtt cac tgg caa 829
Ser Ala Ala Ser Thr Ile Ser Ala His Ser Asn Pro Val His Trp Gln
240 245 250

cac atg gaa acg att gaa ttg gtg aat gat gga tct ggt ttg gga ttt 877
His Met Glu Thr Ile Glu Leu Val Asn Asp Gly Ser Gly Leu Gly Phe
255 260 265

ggc atc ata gga gga aaa gca act ggt gtg ata gta aaa acc att ctg 925
Gly Ile Ile Gly Gly Lys Ala Thr Gly Val Ile Val Lys Thr Ile Leu
270 275 280 285

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Ile Leu Lys Ile Gly Asp Thr Asp Leu Ala Gly Met Ser Ser Glu Gln
305 310 315

gta gca caa gtc ctt agg caa tgt gga aat aga gtt aag ttg atg att 1069

Val Ala Gln Val Leu Arg Gln Cys Gly Asn Arg Val Lys Leu Met Ile

320 325 330

gca aga agt gcc ata gaa gaa cgt aca gca ccc act gct ttg ggc atc 1117

Ala Arg Ser Ala Ile Glu Glu Arg Thr Ala Pro Thr Ala Leu Gly Ile

335 340 345

acc ctc tcc tca tcc cca act tca acg cca gag ttg cgg gtt gat gct 1165

Thr Leu Ser Ser Ser Pro Thr Ser Thr Pro Glu Leu Arg Val Asp Ala

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tct act cag aaa ggt gaa gaa agt gag aca ttt gat gta gaa ctc act 1213

Ser Thr Gln Lys Gly Glu Glu Ser Glu Thr Phe Asp Val Glu Leu Thr

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Lys Asn Val Gln Gly Leu Gly Ile Thr Ile Ala Gly Tyr Ile Gly Asp

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Lys Lys Leu Glu Pro Ser Gly Ile Phe Val Lys Ser Ile Thr Lys Ser

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Ser Ala Val Glu His Asp Gly Arg Ile Gln Ile Gly Asp Gln Ile Ile

415 420 425

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Ala Val Asp Gly Thr Asn Leu Gln Gly Phe Thr Asn Gln Gln Ala Val
430 435 440 445

gag gta ttg cga cat aca gga caa act gtg ctc ctg aca cta atg agg 1453
Glu Val Leu Arg His Thr Gly Gln Thr Val Leu Leu Thr Leu Met Arg
450 455 460

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Lys Asp Ala Asp Leu Ser Pro Val Asn Ala Ser Ile Ile Lys Glu Asn
480 485 490

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Tyr Glu Lys Asp Glu Asp Phe Leu Ser Ser Thr Arg Asn Thr Asn Ile
495 500 505

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510 515 520 525

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Gln Arg Ile Met Gly Ile Asn Tyr Glu Ile Val Val Ala His Val Ser
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655 660 665

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Gln Asp Pro Ile Asp Pro Ala Ser Thr Val Ile Ile Ile Arg Ser Leu
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735 740 745

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830 835 840 845

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850 855 860

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Pro Ser Ser Pro Pro Lys Asp Val Ile Glu Asn Ser Cys Asp Pro Val
880 885 890

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895 900 905

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Glu Arg Gln Asp Glu Asn Thr Pro Ser Val Asp Ile Ser Met Gly Pro
910 915 920 925

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Ala Ser Gly Phe Thr Ile Asn Asp Tyr Thr Pro Ala Asn Ala Ile Glu
930 935 940

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1010 1015 1020

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His Gly Gly Ala Ile Ser Arg Asp Gly Arg Ile Ala Ile Gly Asp Cys
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Tyr Ser Trp Lys Asn Ile Arg Glu Arg Tyr Gly Thr Leu Thr Gly Glu

1265 1270 1275

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Leu His Met Ile Glu Leu Glu Lys Gly His Ser Gly Leu Gly Leu Ser

1280 1285 1290

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1295 1300 1305

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Ile Asp Pro Asn Gly Ala Ala Gly Lys Asp Gly Arg Leu Gln Ile Ala
1310 1315 1320 1325

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Asp Glu Leu Leu Glu Ile Asn Gly Gln Ile Leu Tyr Gly Arg Ser His
1330 1335 1340

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1345 1350 1355

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1505 1510 1515

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1535 1540 1545

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Cys Pro Ile Ile Pro Gly Cys Glu Thr Thr Ile Glu Ile Ser Lys Gly

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1695 1700 1705

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1710 1715 1720 1725

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1730 1735 1740

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1760 1765 1770

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Val Leu Ser

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65 70 75

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80 85 90

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95 100 105

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145 150 155

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175 180 185

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190 195 200 205

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210 215 220

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Arg Gly Ser Leu Pro Gln Leu Val Ser Pro Ile Val Ser Arg Ser Pro
225 230 235

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Ser Ala Ala Ser Thr Ile Ser Ala His Ser Asn Pro Val His Trp Gln
240 245 250

cac atg gaa acg att gaa ttg gtg aat gat gga tct ggt ttg gga ttt 877
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255 260 265

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Gly Ile Ile Gly Gly Lys Ala Thr Gly Val Ile Val Lys Thr Ile Leu
270 275 280 285

cct gga gga gta gct gat cag cat ggg cgt tta tgc agt gga gac cac 973
Pro Gly Gly Val Ala Asp Gln His Gly Arg Leu Cys Ser Gly Asp His
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Ile Leu Lys Ile Gly Asp Thr Asp Leu Ala Gly Met Ser Ser Glu Gln
305 310 315

gta gca caa gtc ctt agg caa tgt gga aat aga gtt aag ttg atg att 1069
Val Ala Gln Val Leu Arg Gln Cys Gly Asn Arg Val Lys Leu Met Ile
320 325 330

gca aga agt gcc ata gaa gaa cgt aca gca ccc act gct ttg ggc atc 1117
Ala Arg Ser Ala Ile Glu Glu Arg Thr Ala Pro Thr Ala Leu Gly Ile
335 340 345

acc ctc tcc tca tcc cca act tca acg cca gag ttg cgg gtt gat gct 1165
Thr Leu Ser Ser Ser Pro Thr Ser Thr Pro Glu Leu Arg Val Asp Ala
350 355 360 365

tct act cag aaa ggt gaa gaa agt gag aca ttt gat gta gaa ctc act 1213
Ser Thr Gln Lys Gly Glu Glu Ser Glu Thr Phe Asp Val Glu Leu Thr
370 375 380

aaa aat gtc caa gga tta gga att acc att gct ggc tac att gga gat 1261
Lys Asn Val Gln Gly Leu Gly Ile Thr Ile Ala Gly Tyr Ile Gly Asp
385 390 395

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Lys Lys Leu Glu Pro Ser Gly Ile Phe Val Lys Ser Ile Thr Lys Ser
400 405 410

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Ser Ala Val Glu His Asp Gly Arg Ile Gln Ile Gly Asp Gln Ile Ile
415 420 425

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Ala Val Asp Gly Thr Asn Leu Gln Gly Phe Thr Asn Gln Gln Ala Val
430 435 440 445

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Glu Val Leu Arg His Thr Gly Gln Thr Val Leu Leu Thr Leu Met Arg
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Lys Asp Ala Asp Leu Ser Pro Val Asn Ala Ser Ile Ile Lys Glu Asn
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Tyr Glu Lys Asp Glu Asp Phe Leu Ser Ser Thr Arg Asn Thr Asn Ile
495 500 505

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Leu Pro Thr Glu Glu Glu Gly Tyr Pro Leu Leu Ser Ala Glu Ile Glu
510 515 520 525

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Gln Arg Ile Met Gly Ile Asn Tyr Glu Ile Val Val Ala His Val Ser
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Lys Phe Ser Glu Asn Ser Gly Leu Gly Ile Ser Leu Glu Ala Thr Val

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Leu Pro Ile Glu Val Thr Met Val Cys Cys Arg Arg Thr Val Pro Pro
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705 710 715

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Gln Asp Pro Ile Asp Pro Ala Ser Thr Val Ile Ile Ile Arg Ser Leu
720 725 730

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735 740 745

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785 790 795

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815 820 825

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Thr Asn Asp Ala Asp Leu Val Asp Glu Ser Thr Phe Glu Ser Pro Tyr
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850 855 860

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865 870 875

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880 885 890

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930 935 940

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Gln Gln Tyr Glu Cys Glu Asn Thr Ile Val Trp Thr Glu Ser His Leu
945 950 955

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1010 1015 1020

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Val Ser Ala Asn Lys Asp Gly Leu Gly Met Ile Val Arg Ser Ile Ile
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1170 1175 1180

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1185 1190 1195

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1200 1205 1210

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1280 1285 1290

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1295 1300 1305

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1330 1335 1340

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1390 1395 1400 1405

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1410 1415 1420

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1470 1475 1480 1485

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1840 1845 1850

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2015 2020 2025

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Lys Pro Pro Ser Gly Gly Leu Gly Phe Ser Val Val Gly Leu Arg Ser
145 150 155

gaa aac aga gga gag ctg gga ata ttt gtt caa gag ata caa gag ggc 589
Glu Asn Arg Gly Glu Leu Gly Ile Phe Val Gln Glu Ile Gln Glu Gly
160 165 170

agt gtg gcc cat aga gat gga aga ttg aaa gaa act gat caa att ctt 637
Ser Val Ala His Arg Asp Gly Arg Leu Lys Glu Thr Asp Gln Ile Leu
175 180 185

gct atc aat gga cag gct ctt gat cag aca att aca cat cag cag gct 685
Ala Ile Asn Gly Gln Ala Leu Asp Gln Thr Ile Thr His Gln Gln Ala
190 195 200 205

atc agc atc ctg cag aaa gcc aaa gat act gtc cag cta gtt att gcc 733

Ile Ser Ile Leu Gln Lys Ala Lys Asp Thr Val Gln Leu Val Ile Ala
210 215 220

aga ggc tca ttg cct cag ctt gtc agc ccc ata gtt tcc cgt tct cca 781
Arg Gly Ser Leu Pro Gln Leu Val Ser Pro Ile Val Ser Arg Ser Pro
225 230 235

tct gca gcc agc aca att tca gct cac tct aat ccg gtt cac tgg caa 829
Ser Ala Ala Ser Thr Ile Ser Ala His Ser Asn Pro Val His Trp Gln
240 245 250

cac atg gaa acg att gaa ttg gtg aat gat gga tct ggt ttg gga ttt 877
His Met Glu Thr Ile Glu Leu Val Asn Asp Gly Ser Gly Leu Gly Phe
255 260 265

ggc atc ata gga gga aaa gca act ggt gtg ata gta aaa acc att ctg 925
Gly Ile Ile Gly Gly Lys Ala Thr Gly Val Ile Val Lys Thr Ile Leu
270 275 280 285

cct gga ggg gta gct gat cag cat ggg cgt tta tgc agt gga gac cac 973
Pro Gly Gly Val Ala Asp Gln His Gly Arg Leu Cys Ser Gly Asp His
290 295 300

att cta aag att ggt gac aca gat cta gca gga atg agc agt gag caa 1021
Ile Leu Lys Ile Gly Asp Thr Asp Leu Ala Gly Met Ser Ser Glu Gln
305 310 315

gta gca caa gtc ctt agg caa tgt gga aat aga gtt aag ttg atg att 1069
Val Ala Gln Val Leu Arg Gln Cys Gly Asn Arg Val Lys Leu Met Ile
320 325 330

gca aga agt gcc ata gaa gaa cgt aca gca ccc act gct ttg ggc atc 1117
Ala Arg Ser Ala Ile Glu Glu Arg Thr Ala Pro Thr Ala Leu Gly Ile
335 340 345

acc ctc tcc tca tcc cca act tca acg cca gag ttg cgg gtt gat gct 1165
Thr Leu Ser Ser Ser Pro Thr Ser Thr Pro Glu Leu Arg Val Asp Ala
350 355 360 365

tct act cag aaa ggt gaa gaa agt gag aca ttt gat gta gaa ctc act 1213
Ser Thr Gln Lys Gly Glu Glu Ser Glu Thr Phe Asp Val Glu Leu Thr
370 375 380

aaa aat gtc caa gga tta gga att acc att gct ggc tac att gga gat 1261
Lys Asn Val Gln Gly Leu Gly Ile Thr Ile Ala Gly Tyr Ile Gly Asp
385 390 395

aaa aaa ttg gaa cct tca gga atc ttt gta aag agc att aca aaa agc 1309
Lys Lys Leu Glu Pro Ser Gly Ile Phe Val Lys Ser Ile Thr Lys Ser
400 405 410

agt gcc gtt gag cat gat gga aga atc caa att gga gac caa att ata 1357
Ser Ala Val Glu His Asp Gly Arg Ile Gln Ile Gly Asp Gln Ile Ile
415 420 425

gca gta gat ggc aca aac ctt cag ggt ttt act aat cag caa gca gta 1405
Ala Val Asp Gly Thr Asn Leu Gln Gly Phe Thr Asn Gln Gln Ala Val
430 435 440 445

gag gta ttg cga cat aca gga caa act gtg ctc ctg aca cta atg agg 1453
Glu Val Leu Arg His Thr Gly Gln Thr Val Leu Leu Thr Leu Met Arg
450 455 460

aga gga atg aag cag gaa gcc gag ctc atg tca agg gaa gac gtc aca 1501
Arg Gly Met Lys Gln Glu Ala Glu Leu Met Ser Arg Glu Asp Val Thr
465 470 475

aaa gat gca gat ttg tct cct gtt aat gcc agc ata atc aaa gaa aat 1549
Lys Asp Ala Asp Leu Ser Pro Val Asn Ala Ser Ile Ile Lys Glu Asn
480 485 490

tat gaa aaa gat gaa gat ttt tta tct tcg acg aga aac acc aac ata 1597
Tyr Glu Lys Asp Glu Asp Phe Leu Ser Ser Thr Arg Asn Thr Asn Ile
495 500 505

tta cca act gaa gaa gaa ggg tat cca tta ctg tca gct gag ata gaa 1645
Leu Pro Thr Glu Glu Glu Gly Tyr Pro Leu Leu Ser Ala Glu Ile Glu
510 515 520 525

gaa ata gaa gat gca caa aaa caa gaa gct gct ctg ctg aca aaa tgg 1693
Glu Ile Glu Asp Ala Gln Lys Gln Glu Ala Ala Leu Leu Thr Lys Trp

530 535 540

caa agg att atg gga att aac tat gaa ata gtg gtg gcc cat gtg agc 1741
Gln Arg Ile Met Gly Ile Asn Tyr Glu Ile Val Val Ala His Val Ser
545 550 555

aag ttt agt gag aac agt gga ttg ggg ata agc ctg gaa gcg aca gtg 1789
Lys Phe Ser Glu Asn Ser Gly Leu Gly Ile Ser Leu Glu Ala Thr Val
560 565 570

gga cat cat ttt atc cga tct gtt cta cca gag ggt cct gtt gga cac 1837
Gly His His Phe Ile Arg Ser Val Leu Pro Glu Gly Pro Val Gly His
575 580 585

agc ggg aag ctc ttc agt gga gac gag cta ttg gaa gta aat ggc ata 1885
Ser Gly Lys Leu Phe Ser Gly Asp Glu Leu Leu Glu Val Asn Gly Ile
590 595 600 605

act tta ctt ggg gaa aat cac caa gat gtg gtg aat atc tta aaa gaa 1933
Thr Leu Leu Gly Glu Asn His Gln Asp Val Val Asn Ile Leu Lys Glu
610 615 620

ctg cct ata gaa gtg aca atg gtg tgc tgt cgt cga act gtg cca ccc 1981
Leu Pro Ile Glu Val Thr Met Val Cys Cys Arg Arg Thr Val Pro Pro
625 630 635

acc acc caa tca gaa ttg gat agc ctg gac tta tgt gat att gag cta 2029

Thr Thr Gln Ser Glu Leu Asp Ser Leu Asp Leu Cys Asp Ile Glu Leu
640 645 650

aca gaa aag cct cac gta gat cta ggt gag ttc atc ggg tca tca gag 2077
Thr Glu Lys Pro His Val Asp Leu Gly Glu Phe Ile Gly Ser Ser Glu
655 660 665

cca gag gat cca gtg ctg gcg atg act gat gcg ggt cag agt aca gaa 2125
Pro Glu Asp Pro Val Leu Ala Met Thr Asp Ala Gly Gln Ser Thr Glu
670 675 680 685

gag gtt caa gca cct ttg gcc atg tgg gag gct ggc att cag cac ata 2173
Glu Val Gln Ala Pro Leu Ala Met Trp Glu Ala Gly Ile Gln His Ile
690 695 700

atg ctg gag aaa ggg agc aaa gga ctt ggt ttt agc att tta gat tat 2221
Met Leu Glu Lys Gly Ser Lys Gly Leu Gly Phe Ser Ile Leu Asp Tyr
705 710 715

cag gat cca att gat cca gca agc act gtg att ata att cgt tct ttg 2269
Gln Asp Pro Ile Asp Pro Ala Ser Thr Val Ile Ile Ile Arg Ser Leu
720 725 730

gtg cct ggc ggc att gct gaa aag gat gga cga ctt ctt cct ggt gac 2317
Val Pro Gly Gly Ile Ala Glu Lys Asp Gly Arg Leu Leu Pro Gly Asp
735 740 745

cga ctc atg ttt gta aac gat gtt aac ttg gaa aac agc agt ctt gag 2365
Arg Leu Met Phe Val Asn Asp Val Asn Leu Glu Asn Ser Ser Leu Glu
750 755 760 765

gaa gct gta gaa gca ctg aag gga gca ccg tca ggg act gtg aga ata 2413
Glu Ala Val Glu Ala Leu Lys Gly Ala Pro Ser Gly Thr Val Arg Ile
770 775 780

gga gtt gct aag cct tta ccc ctt tca cca gaa gaa ggt tat gtt tct 2461
Gly Val Ala Lys Pro Leu Pro Leu Ser Pro Glu Glu Gly Tyr Val Ser
785 790 795

gct aag gag gat tcc ttt ctc tac cca cca cac tcc tgt gag gaa gca 2509
Ala Lys Glu Asp Ser Phe Leu Tyr Pro Pro His Ser Cys Glu Glu Ala
800 805 810

ggg ctg gct gac aaa ccc ctc ttc agg gct gac ttg gct ctg gtg ggc 2557
Gly Leu Ala Asp Lys Pro Leu Phe Arg Ala Asp Leu Ala Leu Val Gly
815 820 825

aca aat gat gct gac tta gta gat gaa tcc aca ttt gag tct cca tac 2605
Thr Asn Asp Ala Asp Leu Val Asp Glu Ser Thr Phe Glu Ser Pro Tyr
830 835 840 845

tct cct gaa aat gac agc atc tac tct act caa gcc tct att tta tct 2653
Ser Pro Glu Asn Asp Ser Ile Tyr Ser Thr Gln Ala Ser Ile Leu Ser
850 855 860

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ctt cat ggc agt tct tgt ggt gat ggc ctg aac tat ggt tct tcc ctt      2701
Leu His Gly Ser Ser Cys Gly Asp Gly Leu Asn Tyr Gly Ser Ser Leu
            865                 870                 875

cca tca tct cct cct aag gat gtt att gaa aat tct tgt gat cca gta      2749
Pro Ser Ser Pro Pro Lys Asp Val Ile Glu Asn Ser Cys Asp Pro Val
        880                 885                 890

ctt gat ctg cat atg tct ctg gag gaa cta tat acc cag aat ctc ctg      2797
Leu Asp Leu His Met Ser Leu Glu Glu Leu Tyr Thr Gln Asn Leu Leu
    895                 900                 905

gaa aga cag gat gag aat aca cct tcg gtg gac ata agt atg ggg cct      2845
Glu Arg Gln Asp Glu Asn Thr Pro Ser Val Asp Ile Ser Met Gly Pro
910                 915                 920                 925

gct tct ggc ttt act ata aat gac tac aca cct gca aat gct att gaa      2893
Ala Ser Gly Phe Thr Ile Asn Asp Tyr Thr Pro Ala Asn Ala Ile Glu
            930                 935                 940

caa caa tat gaa tgt gaa aac aca ata gtg tgg act gaa tct cat tta      2941
Gln Gln Tyr Glu Cys Glu Asn Thr Ile Val Trp Thr Glu Ser His Leu
            945                 950                 955

cca agt gaa gtt ata tca agt gca gaa ctt cct tct gtg cta ccc gat      2989
Pro Ser Glu Val Ile Ser Ser Ala Glu Leu Pro Ser Val Leu Pro Asp
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960 965 970

tca gct gga aag ggc tct gag cac ctg ctt gaa cag agc tcc ctg gcc 3037
Ser Ala Gly Lys Gly Ser Glu His Leu Leu Glu Gln Ser Ser Leu Ala
975 980 985

tgt aat gct gag tgt gtc atg ctt caa aat gta tct aaa gaa tct ttt 3085
Cys Asn Ala Glu Cys Val Met Leu Gln Asn Val Ser Lys Glu Ser Phe
990 995 1000 1005

gaa agg act att aat ata gca aaa ggc aat tct agc cta gga atg aca 3133
Glu Arg Thr Ile Asn Ile Ala Lys Gly Asn Ser Ser Leu Gly Met Thr
1010 1015 1020

gtt agt gct aat aaa gat ggc ttg ggg atg atc gtt cga agc att att 3181
Val Ser Ala Asn Lys Asp Gly Leu Gly Met Ile Val Arg Ser Ile Ile
1025 1030 1035

cat gga ggt gcc att agt cga gat ggc cgg att gcc att ggg gac tgc 3229
His Gly Gly Ala Ile Ser Arg Asp Gly Arg Ile Ala Ile Gly Asp Cys
1040 1045 1050

atc ttg tcc att aat gaa gag tct acc atc agt gta acc aat gcc cag 3277
Ile Leu Ser Ile Asn Glu Glu Ser Thr Ile Ser Val Thr Asn Ala Gln
1055 1060 1065

gca cga gct atg ttg aga aga cat tct ctc att ggc cct gac ata aaa 3325

Ala Arg Ala Met Leu Arg Arg His Ser Leu Ile Gly Pro Asp Ile Lys
1070 1075 1080 1085

att act tat gtg cct gca gaa cat ttg gaa gag ttc aaa ata agc ttg 3373
Ile Thr Tyr Val Pro Ala Glu His Leu Glu Glu Phe Lys Ile Ser Leu
1090 1095 1100

gga caa caa tct gga aga gta atg gca ctg gat att ttt tct tca tac 3421
Gly Gln Gln Ser Gly Arg Val Met Ala Leu Asp Ile Phe Ser Ser Tyr
1105 1110 1115

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Thr Gly Arg Asp Ile Pro Glu Leu Pro Glu Arg Glu Glu Gly Glu Gly
1120 1125 1130

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1135 1140 1145

agg cgg gtg gaa ctc tgg aga gaa cca agc aaa tcc tta ggc atc agc 3565
Arg Arg Val Glu Leu Trp Arg Glu Pro Ser Lys Ser Leu Gly Ile Ser
1150 1155 1160 1165

att gtt ggt gga cga ggg atg ggg agt cgg cta agc aat gga gaa gtg 3613
Ile Val Gly Gly Arg Gly Met Gly Ser Arg Leu Ser Asn Gly Glu Val
1170 1175 1180

atg agg ggc att ttc atc aaa cat gtt ctg gaa gat agt cca gct ggc 3661
Met Arg Gly Ile Phe Ile Lys His Val Leu Glu Asp Ser Pro Ala Gly
1185 1190 1195

aaa aat gga acc ttg aaa cct gga gat aga atc gta gag gtg gat gga 3709
Lys Asn Gly Thr Leu Lys Pro Gly Asp Arg Ile Val Glu Val Asp Gly
1200 1205 1210

atg gac ctc aga gat gca agc cat gaa caa gct gtg gaa gcc att cgg 3757
Met Asp Leu Arg Asp Ala Ser His Glu Gln Ala Val Glu Ala Ile Arg
1215 1220 1225

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Lys Ala Gly Asn Pro Val Val Phe Met Val
1230 1235

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